ASSESSMENT OF EFFECTIVENESS AND SAFETY OF OMALIZUMAB IN THE TREATMENT OF CHRONIC SPONTANEOUS URTICARIA

This dissertation is submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirement of the award for the degree of

M.D BRANCH XX
DERMATOLOGY, VENEREOLOGY AND LEPROSY

STANLEY MEDICAL COLLEGE
CHENNAI – 600 001

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DECLARATION BY THE CANDIDATE

I solemnly declare that the dissertation titled "**Assessment of effectiveness and safety of Omalizumab in the treatment of chronic spontaneous urticaria**" was done by me at Government Stanley Medical College and Hospital during 2015-2018 under the guidance and supervision of my HOD Dr.V.Anandan, M.D., the dissertation is submitted to THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY towards the partial fulfilment of requirement for the award of M.D. Degree(Branch XX) in DERMATOLOGY, VENEREOLOGY AND LEPROSY

Dr. S. Anitha Christy

Place:

Date:

CERTIFICATE BY THE HEAD OF THE DEPARTMENT

Certified that this dissertation entitled **"Assessment of effectiveness and safety of Omalizumab in the treatment of chronic spontaneous urticaria"** is a bonafide work done by **Dr. S. ANITHA CHRISTY** post Graduate Student of the Department of Dermatology, Venerology and Leprosy, Stanley Medical College, Chennai – 600 001 during the academic Year 2015 – 2018. This work has not been submitted previously for the award of any degree.

Dr. V. ANANDAN, M.D.
Head of the Department,
Department of Dermatology,
Stanley Medical College,
Chennai – 600001.

CERTIFICATE BY THE INSTITUTION

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Dr. V. ANANDAN, M.D.
Head of the Department,
Department of Dermatology,
Stanley Medical College,
Chennai – 600001.

Dr. PONNAMBALA NAMASIVAYAM, M.D.
Dean,
Stanley Medical College,
Chennai -600001.

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CONTENTS

INTRODUCTION

Urticaria is transient, well-demarcated, superficial erythematous or pale swellings of dermis, usually very itchy and associated with a surrounding red flare sometimes associated with angioedema.

0.5 -1% of urticaria patients have chronic spontaneous urticaria. Chronic spontaneous urticaria affects the quality of life, causes depression and work absenteeism.

2^{nd} generation antihistamines are the first line of management of chronic spontaneous urticaria. In patients who are not responding to antihistamine, their dose is increased upto four fold.

Omalizumab is the third line of management in patients refractory to the antihistamine treatment of chronic spontaneous urticaria. It is a monoclonal antibody against the free IgE that prevents the binding of IgE Fc εRI receptors in the mast cells, thereby preventing the degranulation of mast cells. It is administered once in 4 weeks and adverse effects are few. The effectiveness is assessed by using Urticaria Activity Score(UAS7).

In this study we administer Inj Omalizumab 300mg subcutaneously once in 4 weeks for 3 cycles and follow up the patient for 12 weeks and assess the effectiveness and safety of omalizumab in chronic spontaneous urticaria patients.

AIM:

To assess the effectiveness and safety of Omalizumab in the treatment of Chronic Spontaneous Urticaria using Urticaria activity score 7 (UAS7).

REVIEW OF LITERATURE

Urticaria is a mast cell driven disease. Rapid appearance of wheals and/or angioedema is a characteristic of urticaria, that is shared by all types of urticaria.

Fig 1: Urticarial plaque over back.

TERMINOLOGY:

WHEAL:

Transient, well-demarcated superficial pink or pale swellings of the dermis due to reversible exudation of plasma in the skin that fade, usually within hours without leaving a mark.

Fig 2: Wheals over knee joint

Three typical features: 1. a central swelling of variable size, almost invariably surrounded by a reflex erythema, 2. associated itching or sometimes burning sensation, and 3.transient nature, with skin returning to its normal appearance usually within 1–24 hours.[1]

ANGIOEDEMA:

Fig 3: Angioedema of lip

Sudden, pronounced deep swelling of lower dermis, subcutaneous or submucosal tissues. They are mostly painful rather than itchy. They are poorly defined and skin coloured. Resolution is slower than for wheals and can take

up to 72 hours.[1]Angioedema without wheals are either mast cell mediated (most common) or bradykinin mediated (less common).

ANAPHYLAXIS:

Acute, severe, life-threatening, generalized or systemic hypersensitivity reaction consists of diffuse erythema, pruritus, urticaria, angio-oedema, hypotension and difficulty in breathing**.**

HISTORY

The history of urticaria is fascinating and it partly reflected by many different names in the past. The earliest description of urticaria is found in Chinese tome. They used the term 'Feng Yin Zheng'(wind type concealed rash). The 'Urtica' is the Latin word for nettles. In 4th century Hippocrates recognised the association of urticaria with nettles. 'Urticadioica'- Sting of nettle.

The Romans focused on the burning (urere) at sites of wheals and Plinius introduced the name 'Uredo' meaning burning. In the 10th century, Hali Ben Abbas termed 'Essera' meaning mountain or elevation. In Indian Ayurvedic literature, it is 'sheeta pitta', meaning urticaria. In 18th century, Zedler termed the disease 'Urticatio' and in 1792 Frank coined the term 'Urticaria'.

Borsch described Solar urticaria in 1719. Dermographism was first described by Heberden in 1767. Urticariapigmentosawas described by Edward

Nettleship (1869) and named by Sangster. Mast cells in lesions were described by Unna. Cholinergic urticaria was described by Duke in 1924. Shelley &Rawnsley in 1964coined Aquagenic urticaria and Shelley & Shelley in 1985 termed Adrenergic urticaria. In 1882 Quincke described angioedema. In 1885 Osler described cases of Hereditary angioedema. H1 anti histamines were discovered in 1937 by Bovet and Staub.

EPIDEMIOLOGY

INCIDENCE:

One in five of the general population may develop urticaria in their life time.

PREVALENCE:

Global prevalence of chronic spontaneous urticaria is 0.5% -1%.[2] It constitutes two third of the cases of chronic urticaria.

AGE:

Acute urticaria occurs more common in children. Chronic spontaneous urticaria affects all age groups but more common in second to fourth decades.[3]

SEX:

Women to men ratio is 2:1 with chronic spontaneous urticaria.[3]No sex predilection is seen in acute spontaneous urticaria and inducible urticaria.

ASSOCIATED DISEASES:

Acute urticariais commonly associated with upper respiratory tract viral infections, streptococcus pyogenes and Anisakis simplex.

Chronic urticariais associated with helminthic infestations,[5] active Helicobacterpylori infections[6], coeliac disease in children[7], dental and ENT infections, Candida infections of bowel, auto immune thyroid disease[8], haematological malignancies and lymphoma.[9]

PATHOPHYSIOLOGY:

Urticarial skin lesions show recruitment of mast cells, basophils, neutrophils, eosinophils and T lymphocytes.[1,10-14]

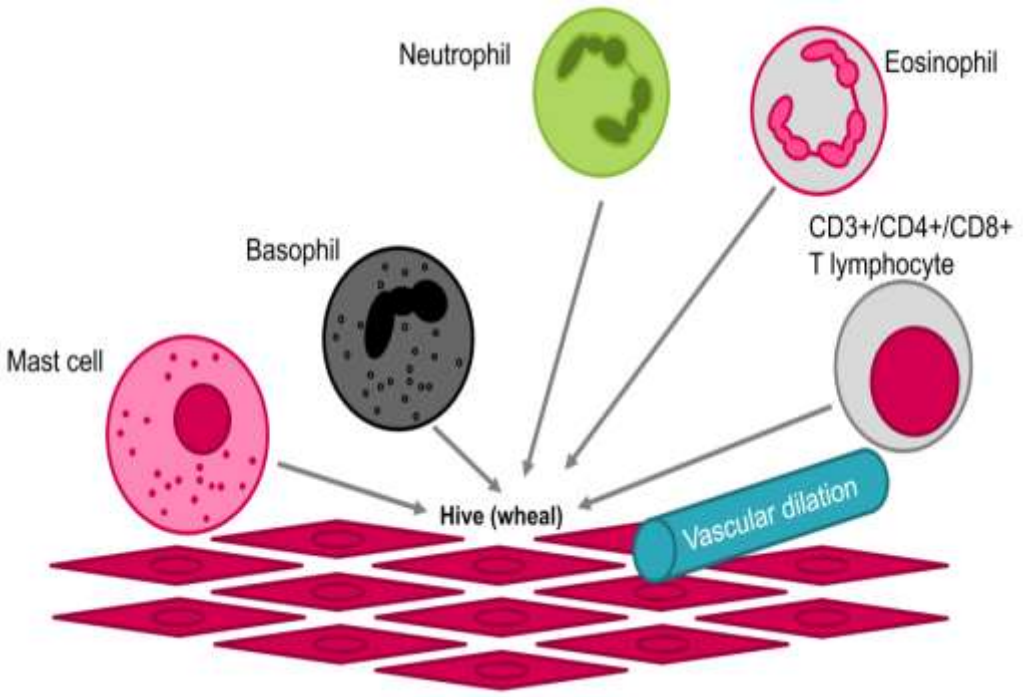


Fig: Inflammatory mediators of urticaria

Various pathways involved in the pathogenesis of urticaria are[15]

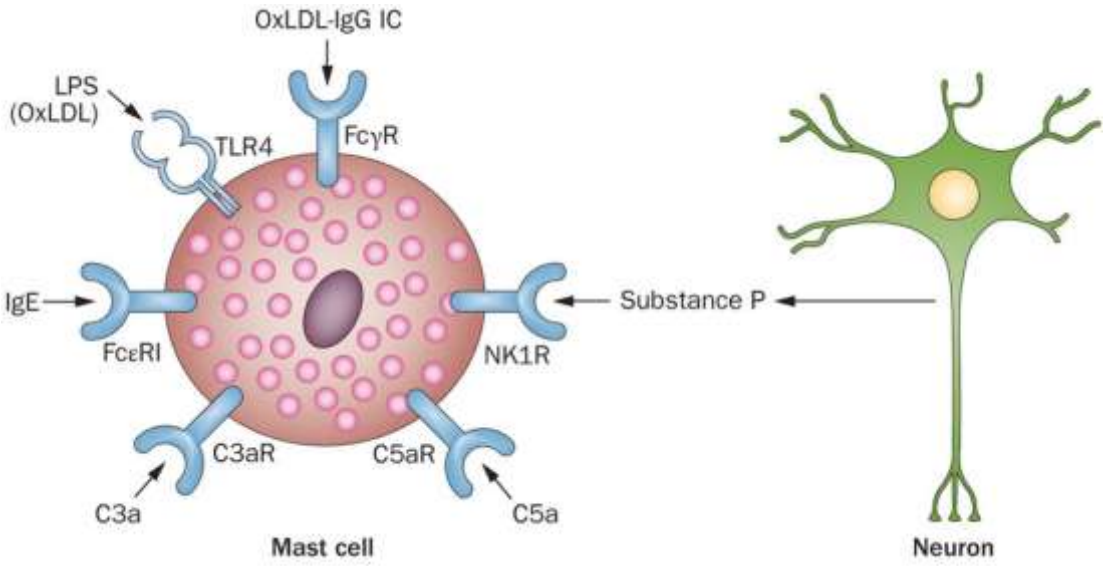


Fig: various pathways of urticaria

- IgE or IgE receptor pathway,
- Complement system,
- Arachidonic acid pathway,
- Direct mast cell degranulation

Crosslinking of mast cell bound specific immunoglobulin E (IgE) by exogenous allergens may cause acute spontaneous urticaria. Binding of pathogen associated molecular patterns (PAMPs) on microbes to Toll-like receptors on mast cells may be the pathogenesis of acute urticaria.

C5a complement is a co-factor for mast cell degranulation in vitro.[16] Tryptase is released in conjunction with histamine. It can induce mast cell degranulation and cleave C3 to C3a and C3b. C3a can activate mast cells, and C3b can activate the alternative complement pathway.

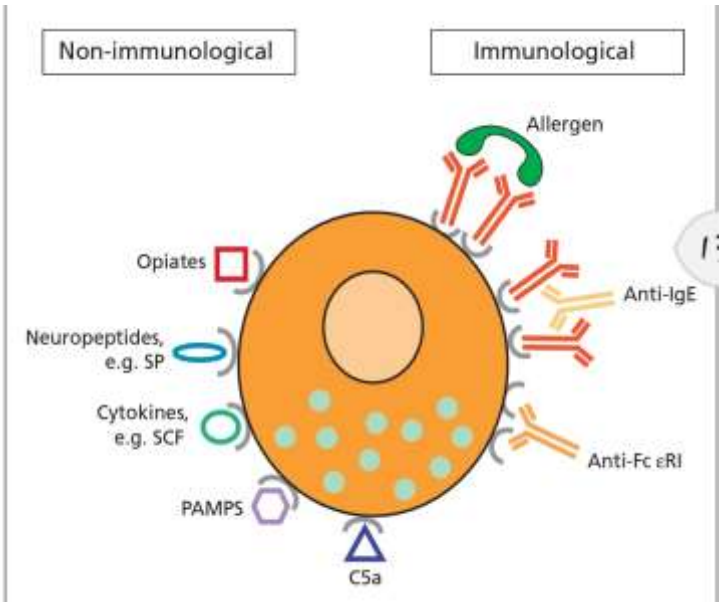


Fig: Factors in the pathogenesis of urticaria

Degranulation of mast cells and basophils by immunological or non-immunological mechanism is the final step in the pathogenesis of urticaria.

MEDIATORS FOR URTICARIA AND ANGIOEDEMA:

PREFORMED MEDIATORS:

- Histamine
- Tumour necrosis factorαrecruit acute inflammatory cells, neutrophils and eosinophils into wheals.

NEWLY FORMED MEDIATORS:

- Prostaglandin D2
- Platelet activating factors
- Basophils cause prolongation of wheal response
- Interleukin 8
- Interleukin 10

ROLE OF HISTAMINE & IT'S RECEPTORS IN URTICARIA:

HISTAMINE:

It is synthesized by mast cells and basophils. It is released due to variety of stimuli. It mediates itching primarily by H_1 receptor on the C nerve fibers which is a G protein coupled receptor attached to phospholipase C*B*3. It is the primary mediator in urticaria, mastocytosis, insect bite reactions and allergic drug reaction. It has four receptors in our body.

H1 RECEPTORS:

These receptors are located in smooth muscle cells, endothelium and central nervous system. They cause bronchoconstriction, vasodilatation, itch, flare, erythema, wheals, sleep and appetite suppression.

H2 RECEPTORS:

These receptors are located mainly in gastric parietal cells, vascular smooth muscle cells and keratinocytes. They are responsible for erythema, wheals and gastric acid secretion.

H3 RECEPTORS:

These receptors are seen in nervous system as inhibitory auto receptors and they decrease neuro transmitter release. These receptors are not found in human skin.

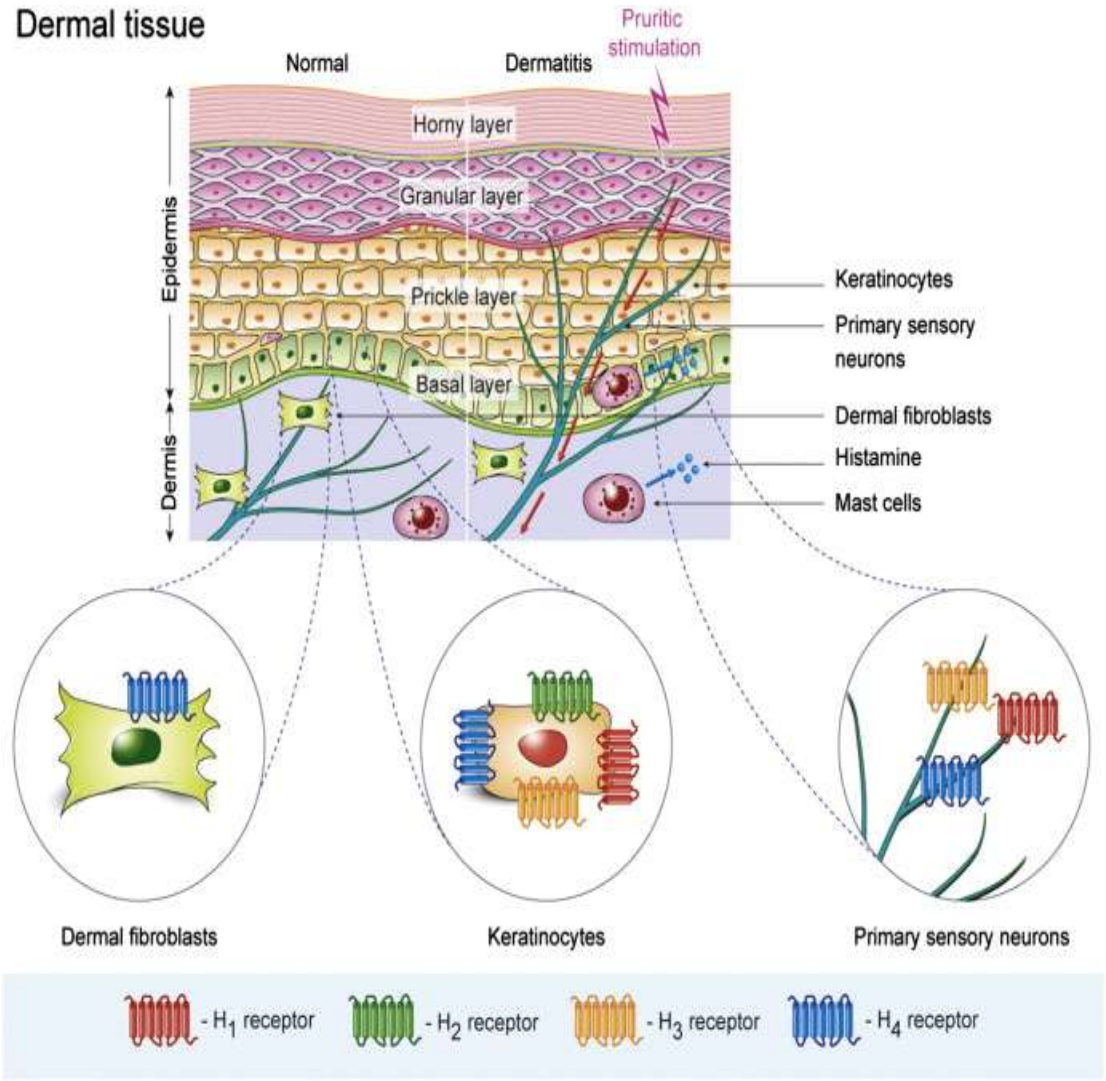


Fig: location of histamine receptors in skin

H4 RECEPTORS:

These receptors are found in eosinophils, basophils, mast cells and dendritic cells as well as bone marrow. They play an active role in chemotaxis. Activation of this receptor causes scratching behaviour in mice.

GENETIC PREDISPOSITION:

Till date no predisposing factors for the development of spontaneous or inducible urticaria have been reported though several polymorphisms seems to be linked to aspirin-sensitive urticaria. There are very strong associations between patients with functional autoantibodies and HLA-DR4 in chronic spontaneous urticaria.

CLASSIFICATION OF URTICARIA[1]:

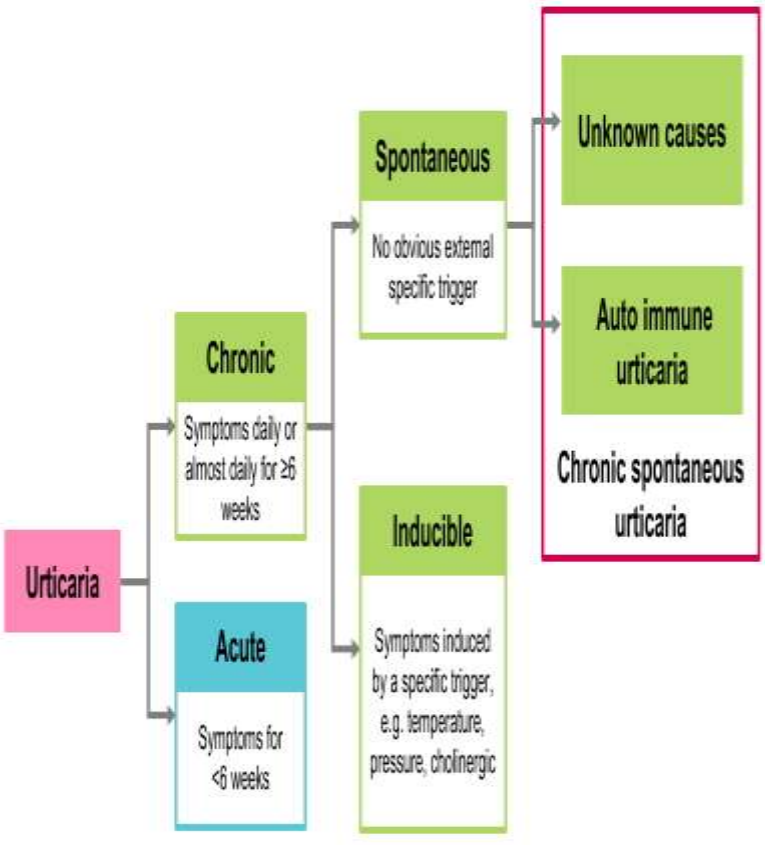


Fig: Classification of urticaria

CLASSIFICATION OF CHRONIC URTICARIA[1]:

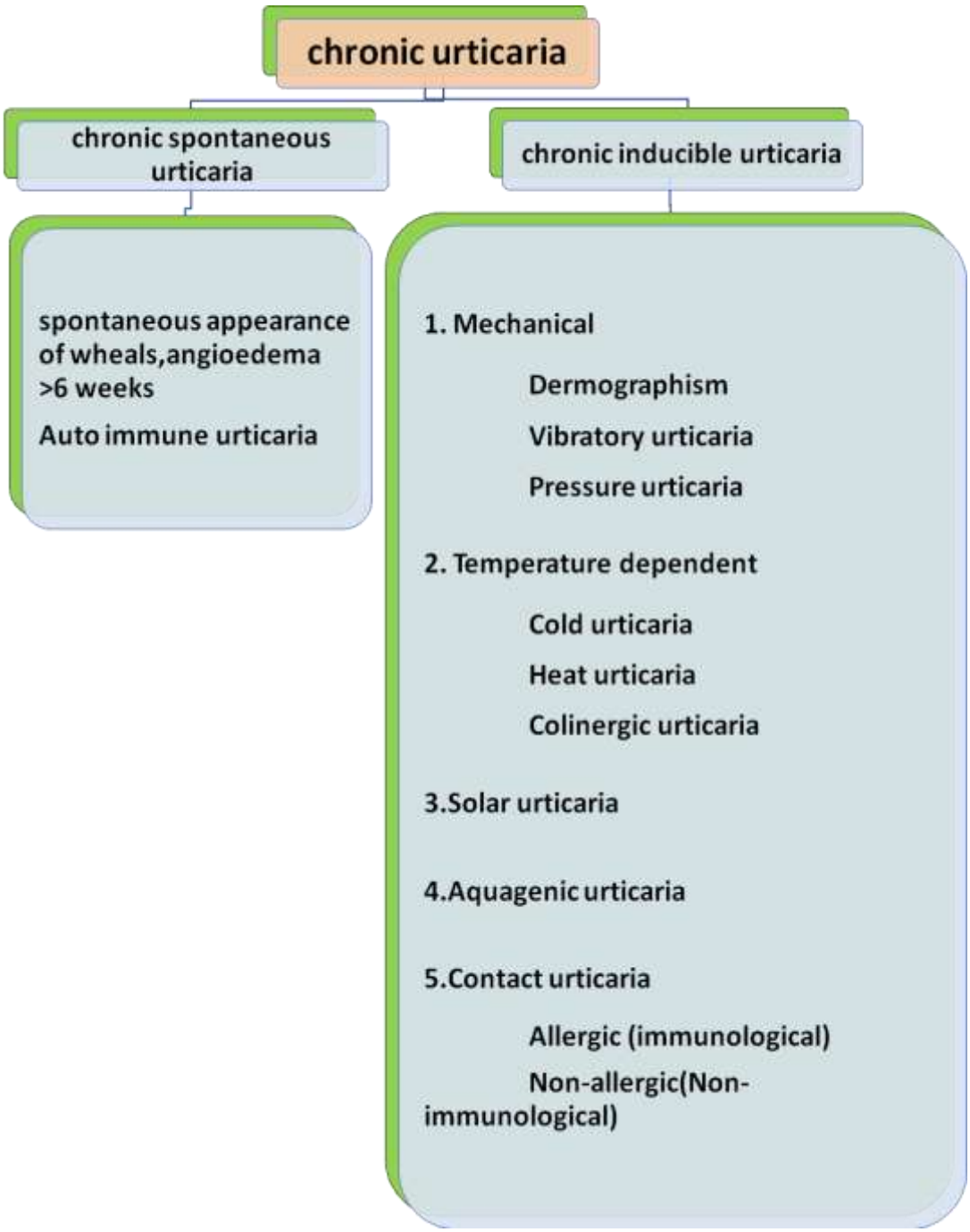


Fig: Classification of chronic urticaria

ACUTE SPONTANEOUS URTICARIA:

ETIOLOGY:

- Idiopathic
- Infections
- Viral - upper respiratory tract infections, hepatitis B and C
- Bacterial - Streptococcus pyogenes
- Parasitic -Anisakis simplex
- Foods - cow's milk, hen's egg, nuts, seeds
- Drugs– β-lactam antibiotics, aspirin
- Stings - bee, wasp venoms
- Blood products - transfusions
- Vaccines
- Contactants - latex

CHRONIC INDUCIBLE URTICARIA:

DERMOGRAPHISM:

On stroking the skin there will be TRIPLE RESPONSE of local erythema due to capillary vasodilation, followed by edema and a surrounding flare due to axon reflex-induced dilatation of arterioles.

Fig: Dermographism

Pathogenesis:

Mast cells sensitised with immunoglobulins(IgE) react with neoantigen induced by mechanical stimulation of skin resulting in release of mediators.

Types of dermographism:

1. Red dermographism – appears following rubbing instead of stroking.
2. Cholinergic dermographism - it resembles multiple small urticarial papules of cholinergic urticaria.
3. Delayed dermographism- it appears after 3-6 hours and persist upto 48 hours. It is usually tender.
4. White dermographism- it occurs due to capillary vasoconstriction following light stroking. It is seen in normal people but more pronounced in atopic dermatitis.
5. Black dermographism– the discolourisation is due to pressure from metallic objects.

VIBRATORY URTICARIA:

They are described as an autosomal dominant familial form but an acquired form is seen occasionally. Any vibratory stimulus like jogging, vigorous towelling induces localised urticaria within minutes, lasting for few hours.

PRESSURE URTICARIA:

Immediate:

Wheal occurs within minutes of applying perpendicular pressure to the skin and persist for 30 min to few hrs. eg., leaning against furniture,handling a steering wheel, crossing legs.

Delayed (DPU):

It appears after a delay of 30 min to 9 hrs and lasts upto 12 to 72 hrs. They are itchy and often tender over soles and scalp. Urticaria appear at the site of tight clothing (waist line), hands after manual works, prolonged sitting on buttocks and lower back and feet on walking. Pressure exacerbates chronic spontaneous urticaria to some extent. It is associated with systemic symptoms like malaise, arthralgia as well as with delayed dermographism and cold urticaria.

Fig: Pressure urticaria

HEAT URTICARIA:

Heat urticaria is the rarest form of physical urticaria. It is more common in women. Localized warming of skin at temperatures around 38 to 44° C induces wheals. It starts in 2-5 min and last for 1-3 hours.

COLD URTICARIA:

Primary cold urticaria:

Commonest form occurring in young adults. Itching and wheals occur within minutes of exposure to cold. Cold rain and cold wind are effective stimuli. Systemic symptoms like flushing, palpitations, headache, wheezing, loss of consciousness and drowning may occur.

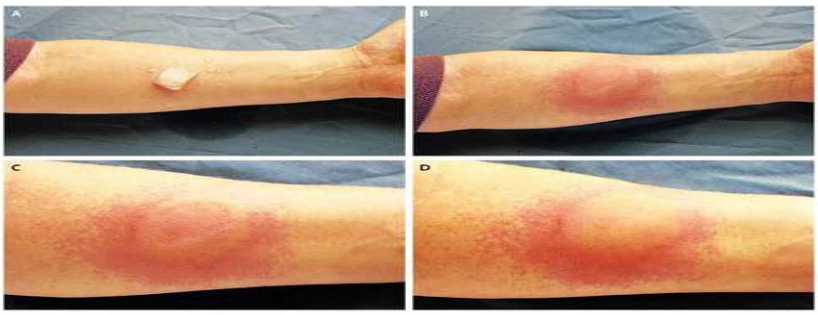


Fig: Demonstration of cold urticaria

Secondary cold urticaria:

This type of cold urticaria is secondary to cryoproteins. It is associated with other conditions like Raynaud phenomenon, purpura or skin necrosis.

Systemic cold urticaria:

Generalised wheals occurs in response to cooling of the core body temperature.

COLINERGIC URTICARIA:

It accounts for 5% of chronic urticaria and is common in adolescents and more common during winter. Wheals appear after sweating and is due to stimulation of the cholinergic postganglionic sympathetic nerve supply to the sweat glands.

SOLAR URTICARIA:

On exposure to visible, long or short wave UV radiations, wheals appear with in minutes at exposure sites but disappear within 2 hours.

a. Primary– it is idiopathic. It is more common in women and systemic symptoms are seen in severe cases.

b. Secondary- it occurs secondary to porphyria cutaneatarda, erythropoietic porphyria, systemic lupus erythematosus and drugs like tetracycline, chlorpromazine.

c. Delayed type

d. Fixed solar urticaria- it is inducible at particular wave length between 300-700nm.It is idiopathic but sometimes occurs secondary to porphyria.

AQUAGENIC URTICARIA:

Occurrence of wheals with wide flare on contact with water of any temperature. It usually disappears in 30-60 minutes after contact with water. Other urticaria induced by water are cold urticaria, cholinergic urticaria and dermographism. Aquagenic pruritis without wheals occurs over the legs and lower trunk.

CONTACT URTICARIA:

Allergic type:

In an individual who has already developed specific IgE to an allergen contact will elicit type 1 hypersensitivity response which causes mast cell degranulation with release of histamine causing wheal and flare. The commonest cause are latex and food like nuts, fruits, fish.

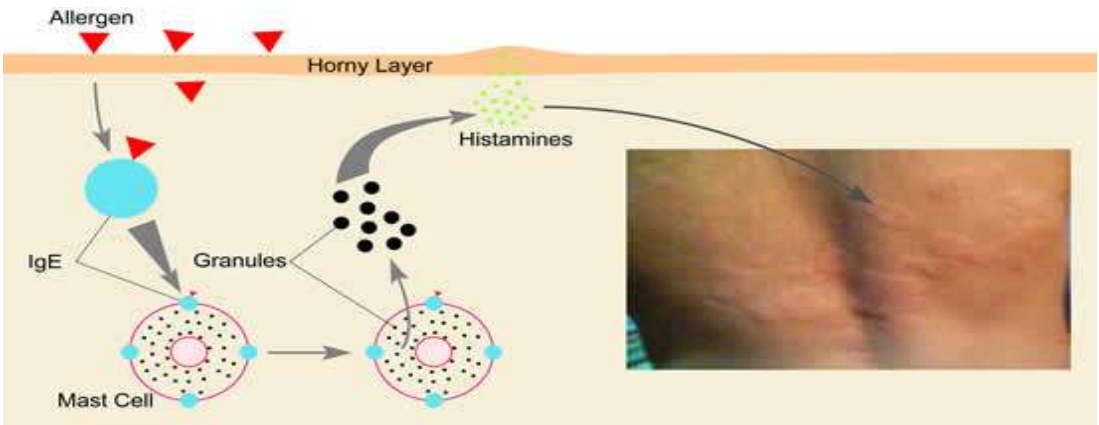


Fig: Pathogenesis of allergic type of contact urticaria

Non allergic type:

It is caused by direct injection of vasoactive chemical by plants or animals or exposure to cosmetics (cinnamic aldehyde, balsam of Peru) or food additives (benzoicacid, sorbic acid). This is due to the formation of prostaglandin D2 and not histamine release.

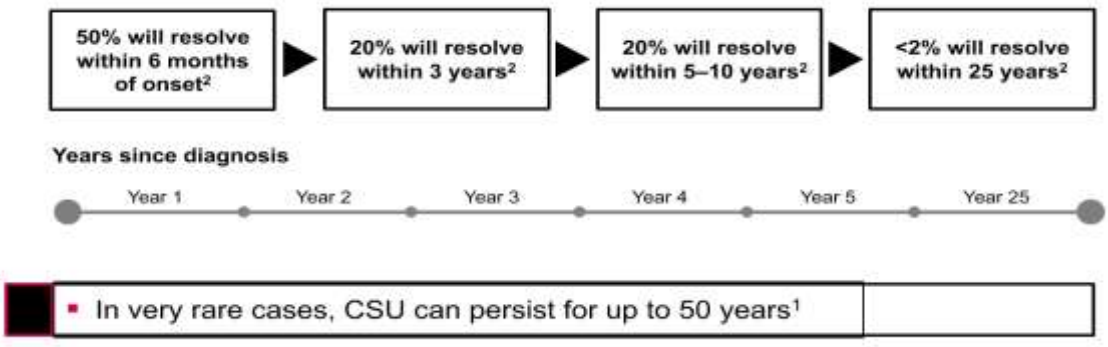
CHRONIC SPONTANEOUS URTICARIA:

Based on EAACI/GA2LEN/EDF/WAO guidelines,

Chronic spontaneous urticaria is defined as spontaneous (without external physical triggers), sudden appearance of wheals, and/or angioedema lasting more than 6 weeks duration.[3]

NATURAL COURSE OF CHRONIC SPONTANEOUS URTICARIA:

Duration of CSU is estimated to be 1-5 years of diagnosed CSU population:[3,17]



DEFINITION OF REFRACTORY CHRONIC SPONTANEOUS URTICARIA:

Chronic spontaneous urticaria that does not respond to standard of care, is labelled as refractory urticaria.[11] The standard of care for chronic spontaneous urticaria is the non-sedating H1antihistamines (cetirizine, loratadine, fexofenadine, etc.). The duration of non-response to standard of care has to be at least 2 weeks to classify the patient as refractory chronic spontaneous urticaria.

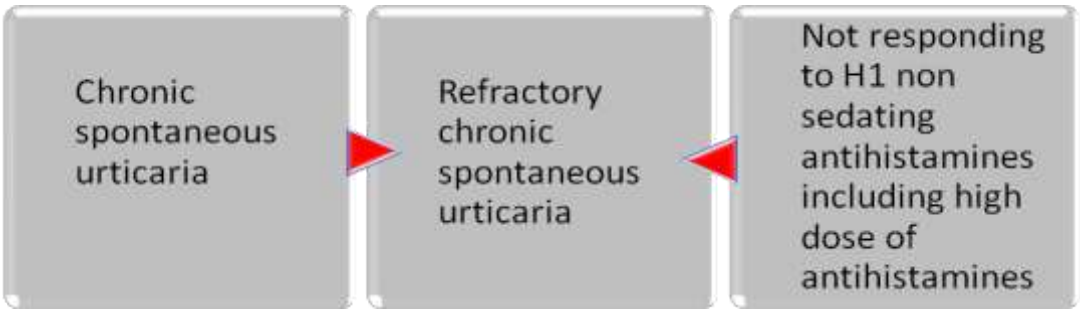


Fig: Refractory chronic spontaneous urticaria

IMPACT OF URTICARIA ON QUALITY OF LIFE(QOL):

QOL is affected in chronic spontaneous urticaria due to its impact on the activities of daily living, self-perception, social aspects, treatmentrelated effects, and mainly the psychological status of the patient.[21] The psychological aspects of QOL contribute to work productivity, absenteeism and thereby have financial implications. Occurrence of angioedema further impairs the quality of life.[22]

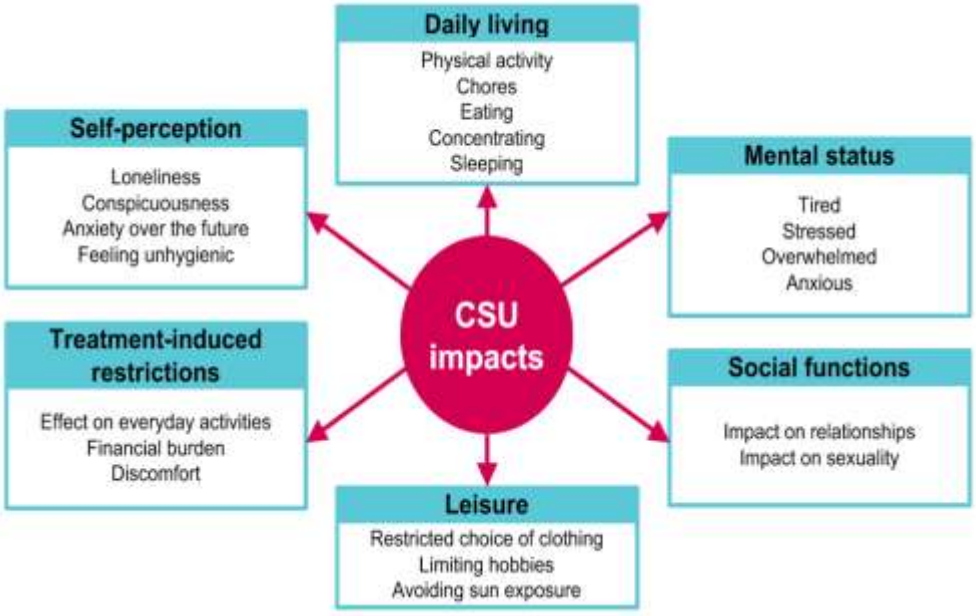


Fig: Factors impact the quality of life in CSU

PROGNOSTIC FACTORS FOR CSU DURATION:

- More severe disease[3,18]
- Concurrent angioedema[3,18]
- Concurrent inducible urticaria[3,19]
- A positive autologous serum skin test[3,20]

PATHOGENESIS OF CHRONIC SPONTANEOUS URTICARIA(CSU):

Although the exact trigger of CSU is unknown, it is hypothesized that there is a repeated and extensive activation of the dermal mast cells.[23] This leads to degranulation of cutaneous mast cells and the release of histamine (preformed) and other mediators (newly formed) such as prostaglandins, endogenous peptides, endorphins, and enkephalins.[24] This causes wheal

formation, vasodilatation, and erythema. Histamine released from the mast cells, prostaglandins, endogenous peptides, endorphins, enkephalins, and also chemoattractant from other cells such as neutrophils also mediate in the process of wheal formation.

The threshold for mastcell activation and degranulation is lowered in patients with CSU. Autoimmune mechanisms are involved in CSU in about 45% cases and the remaining 55% remain idiopathic.[25] Either IgG autoantibodies to the alpha subunit of the Fc receptor of the IgE molecule or anti-IgE autoantibodies can activate basophils to release histamine. These antibodies are reported to be specific to CSU.[26,27]

Antithyroid antibodies are reported to be positive in 27.3% (33% males and 25% females) of patients with chronic spontaneous urticaria.[28]

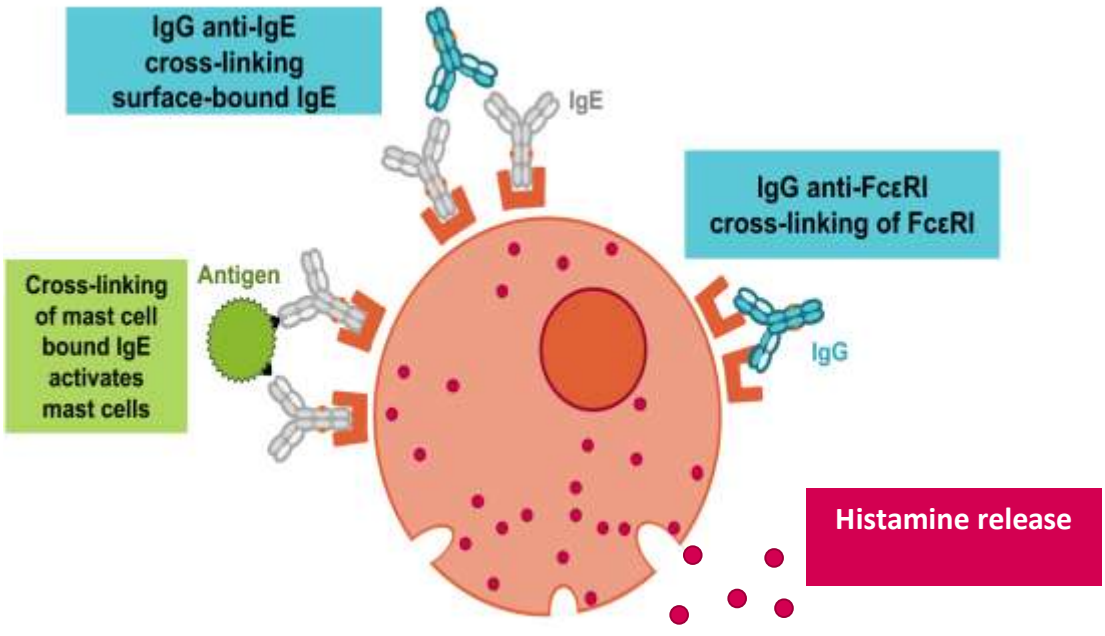
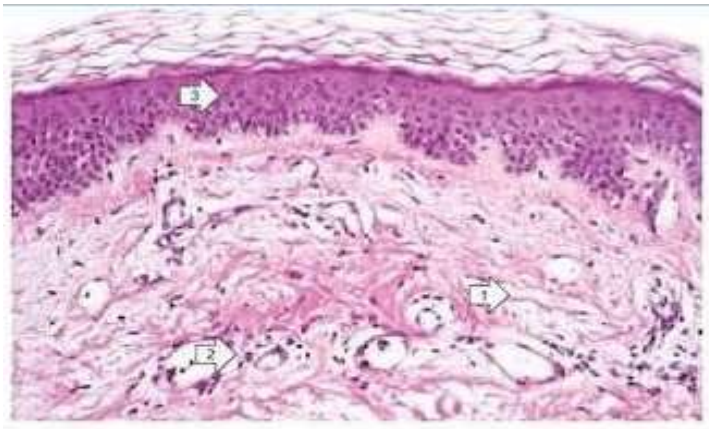


Fig: Mast cell activation in CSU

Angioedema rarely occurs in isolation in chronic spontaneous urticaria[29,30] and it results from release of inflammatory mediators (histamine, cytokines) after mast cell degranulation.[23,24]

HISTOPATHOLOGY:

The histopathologic features show non-specific changes in urticaria. Acute urticaria shows dilated venules, endothelial swelling. In chronic urticaria dermis shows features of perivascular & interstitial infiltrate (lymphocytes, eosinophils, neutrophils). On electron microscopy, dermal mast cells show signs of degranulation.



1. Superficial dermal edema (space between collagen)
2. Dilated blood vessels with perivascular inflammatory cells
3. Normal Epidermis (no spongiosis or hyperplasia)

DIFFERENTIAL DIAGNOSIS:

The possible differential diagnosis are:

HIVES	**ANGIOEDEMA**
▪ Acquired auto inflammatory disorders eg. o Schnitzler´s syndrome o systemic-onset juvenile idiopathic arthritis o adult-onset Still's disease ▪ Hereditary autoinflammatory disorders eg. o Cryopyrin associated periodic syndromes such as ▪ familial cold auto-inflammatory syndromes ▪ Muckle-Wells syndrome ▪ neonatal onset multisystem inflammatory disease ▪ hyper-IgD syndrome ▪ TNF receptor alpha-associated periodic syndrome ▪ Urticarial vasculitis	▪ Hereditary angioedema ▪ Acquired angioedema due to C1-inhibitor deficiency ▪ Angiotensin converting enzyme nhibitor- induced angioedema

Table 1: Differential diagnosis of urticaria

URTICARIAL VASCULITIS:

This is the most common differential diagnosis for chronic urticaria. It is characterized clinically by presence of urticarial wheals for >24 hrs. It is Type III hypersensitivity reaction. It is more common in middle aged women. It

manifests as burning and pain rather than itching. Trunk and proximal extremities are commonly involved. It resolves with residual staining.

Hypocomplementic urticarial vasculitis syndrome (HUVS):

It is associated with connective tissue diseases (SLE, Sjogren's), viral infections (Hep B&C, EBV), neoplasms (IgM gammopathies), drugs (NSAIDS, KI, fluoxetine). It has systemic features like migratory arthralgia (50%), lymphadenopathy, hepatosplenomegaly, respiratory, GIT, renal and ocular manifestations. Complement level is the indicator of severity & marker for prognosis. Low C1q, C4 (occasionally C3, C5, CH50), presence of anti C1q auto antibody and lowC1q level seen in 100% pts of HUVS

Normocomplementic urticarial vasculitis syndrome(NUVS):

It is common (70-80%) and limited to the skin. High erythrocyte sedimentation rate and microscopic proteinuria are seen.

Urticaria	Urticarial vasculitis
Lasts < 24 hrs.	> 24 hrs.
More itching.	burning, painful and tender.
Recur at different sites.	may recur at same sites.
Systemic features not uncommon.	common.
Etiology- variable.	CTD, infections, malignancy.
No residual pigmentation.	Dusky hue staining.
HPE- non-specific.	Features of vasculitis.
Treatment-antihistamines	Dapsone, Hydroxychloroquin, colchicin

Table 2: Difference between urticaria and urticarial vasculitis

DIAGNOSTIC ALGORITHM OF CHRONIC SPONTANEOUS URTICARIA:[1]

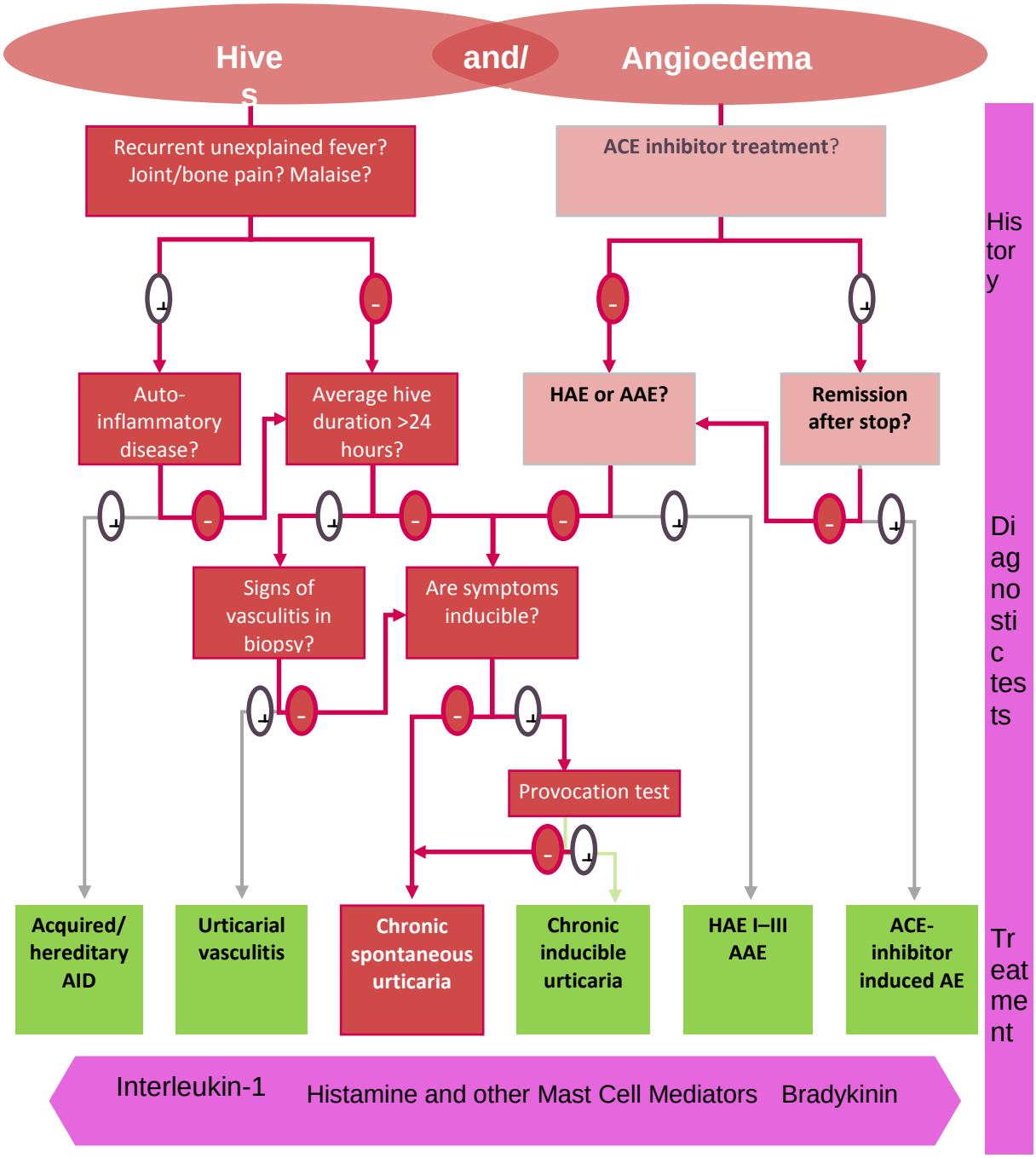


Fig: EAACI/GA[2]LEN/EDF/WAO urticaria guidelines: Diagnostic algorithm.

DIAGNOSIS OF CHRONIC SPONTANEOUS URTICARIA:

Thorough history and physical examination is the most important diagnostic procedure.

- H/O urticaria - timing, frequency and duration of attacks;
- H/O wheals -shape, size, distribution and associated symptoms of lesions;
- Family history
- Medical history, including allergies; correlation to any triggers, e.g., food, exercise, drug use;
- H/O aggravating factors like work, hobbies, smoking habits, and stress;
- Previous therapy and response to treatment;
- H/O to exclude physical urticaria, urticarial vasculitis, and inducible urticaria.

INVESTIGATIONS:

- Blood haemoglobin,
- Differential blood count,
- Erythrocyte sedimentation rate,
- Absolute eosinophil count,
- Serum IgE levels,
- Liver function test,
- Renal function test,

- Anti nuclear antibody,
- C‑ reactive protein,
- ELISA for HIV,
- RPR for syphilis,
- HBsAg and anti-HCV,
- Chest X-ray and Mantoux test,
- ECG and Echocardiograph,
- Stool for ova and cyst,
- Thyroid profile,
- Anti-thyroid antibodies,
- Autologous serum skin test,
- ENT, Dental, cardiology and chest physician opinions are obtained.

AUTOLOGOUS SERUM SKIN TEST(ASST):

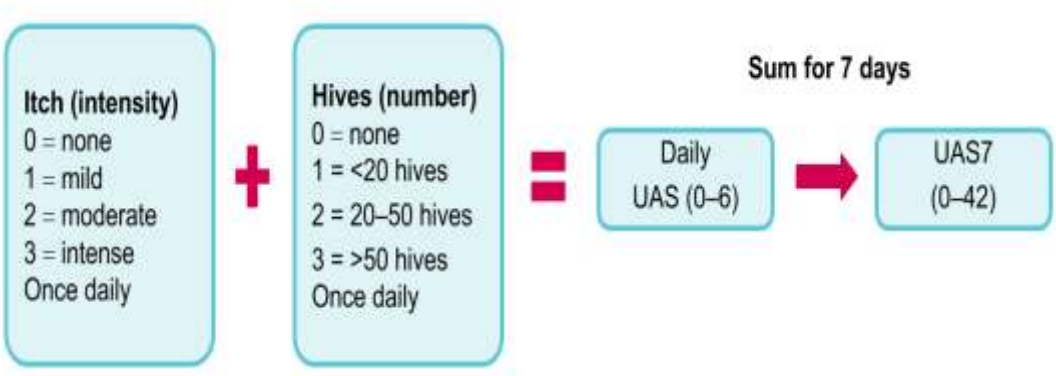
1986, Grattan et al were the first to use ASST to differentiate autoimmune urticaria from chronic spontaneous urticaria. The patient was injected intradermal 0.1 ml of autologous serum and normal saline as control. The positive results were arbitrarily defined as formation of a wheal by serum within 2 h of injection that is at least 5 mm larger than that resulting from saline control and had a difference of 10 mm in the diameter of surrounding erythema. ASST positivity indicates auto immune urticaria. ASST results tend to get modified with treatment. The patients should not take antihistamines for

at least 2-3 days, long-acting antihistamine for 7 days prior to the test to avoid false negative results.

URTICARIA ACTIVITY SCORE -7(UAS7):

SCORE		WHEALS SCORE	ITCH SEVERITY SCORE (ISS)
0	NONE	**None**	**None**
1	MILD	**<20 wheals/24 h**	**Present but not annoying or troublesome**
2	MODERATE	**20–50 wheals/24 h**	**Troublesome but does not interfere with normal daily activity or sleep**
3	INTENSE	**>50 wheals/24 h or large confluent areas of wheals**	**Severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep**

UAS7 is a weekly composite score of the itch severity score (ISS) and number of hives score (0-42) and used to measure disease activity.[1,31]



- Weekly itch severity score is the sum of daily ISS over 7 days.
- Weekly number of hives score is the sum of the daily number of wheals score over 7 days.

CATEGORIZATION OF SEVERITY

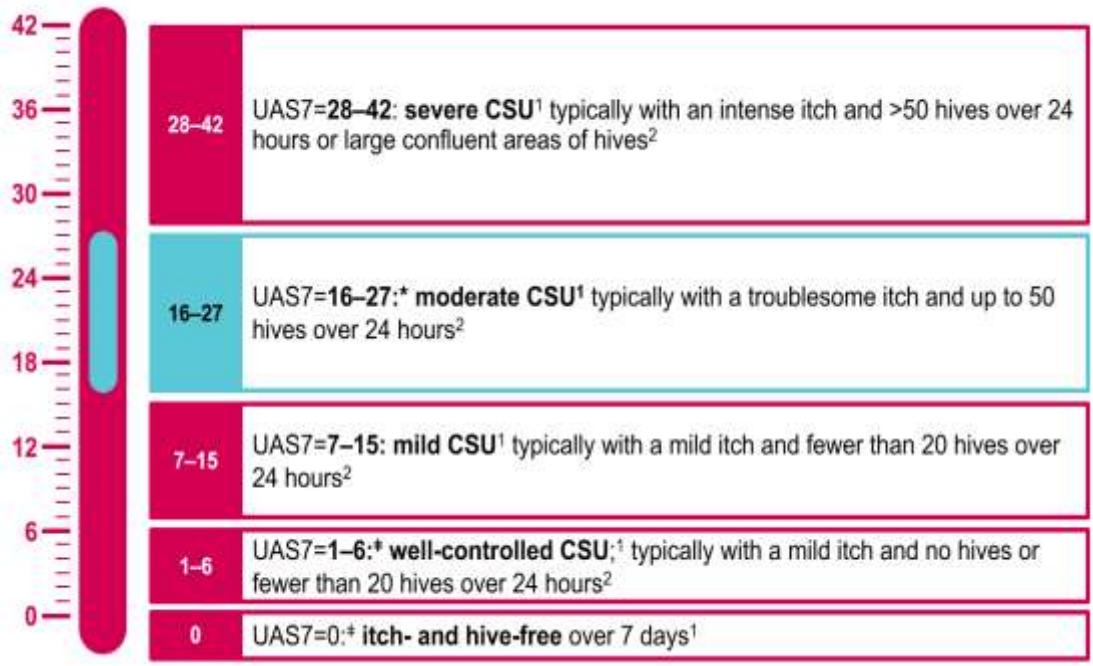
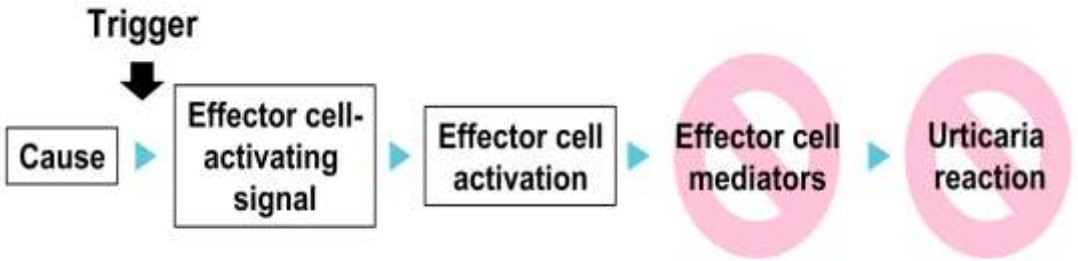


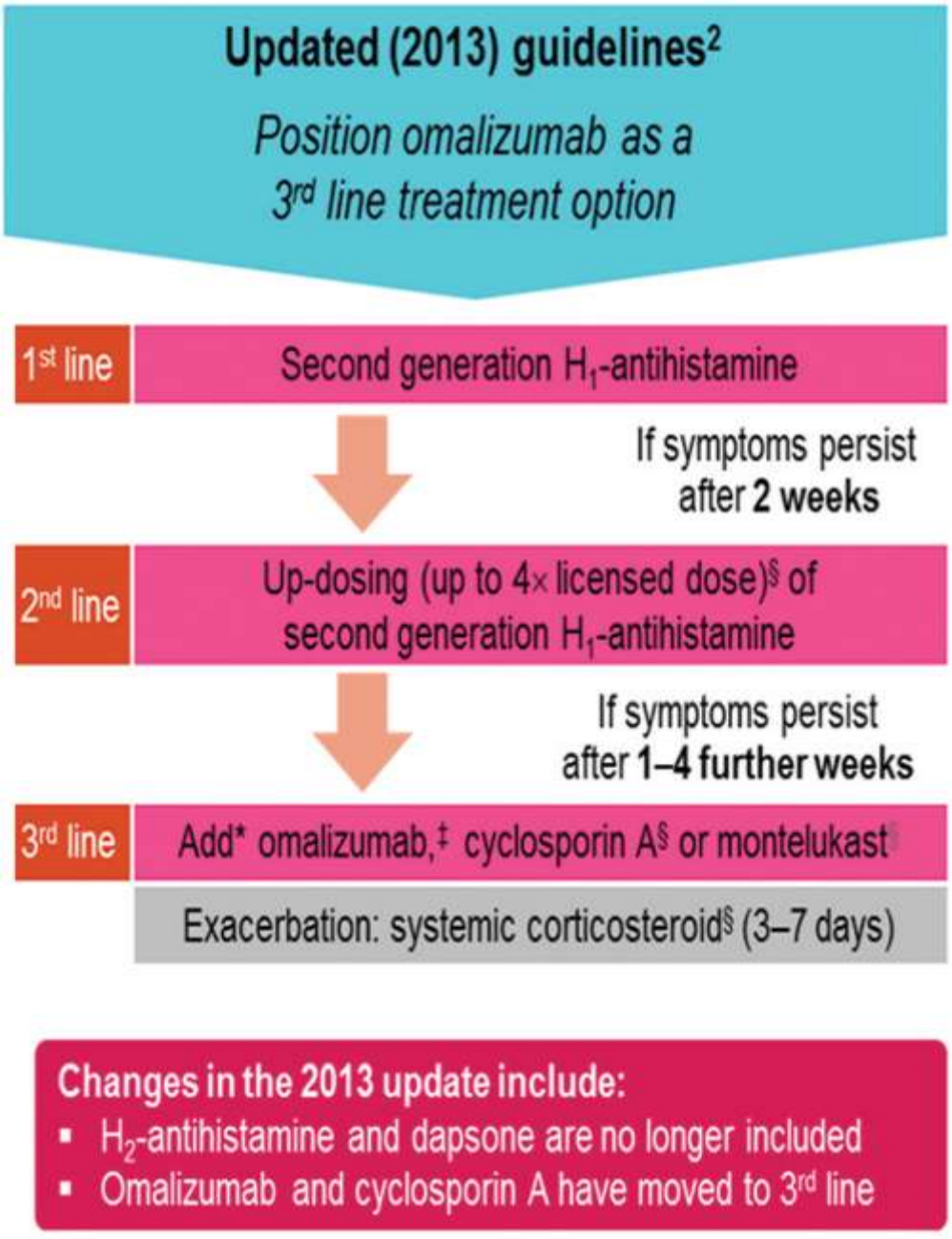
Fig: Categorization of severity of CSU

AIM OF TREATMENT:

The main aim is to decrease the effect of mast cell and/or basophil mediators on the target organs leading to the symptoms of urticaria.[1,3]



TREATMENT ALGORITHM FOR CHRONIC SPONTANEOUS URTICARIA IN INDIA:



1ST LINE OF MANAGEMENT OF CHRONIC SPONTANEOUS URTICARIA:

SECOND GENERATION H1 ANTIHISTAMINES:

These are the first line treatment for all patients with chronic spontaneous urticaria.[1] They are rapidly absorbed, reaches peak serum concentration in 1-3 hrs. Second generation non sedative H1 antihistamines are now the treatment of choice.

Advantages:

- Non sedative at recommended doses.
- Minimal anticholinergic side effects.

2nd generation anti histamines are:

- Cetirizine
- Levocetrizine
- Loratadine
- Desloratadine
- Fexofenadine
- Mizolastine
- Rupatadine.

CETRIZINE:

Cetrizine is given as 10mg/day. It is poorly metabolized in liver and elimination is through urine. It is rapid absorbed. Its enantiomer levocetrizine is also used in the treatment of chronic spontaneous urticaria. Cetrizine may cause

sedation at therapeutic as well as supra therapeutic dose, whereas levocetirizine does not have the potential of causing sedation at supratherapeutic dose.

LORATADINE:

Loratadine is prescribed in the dose of 10mg daily and it is metabolized in the liver by CYP3A4. Desloratadine is given in the dose of 5mg daily. Desloratadine is non sedative.

FEXOFENADINE:

Fexofenadine with adult dose of 180mg/day is the active metabolite of terfenadine but without cardiotoxicity at clinically relevant doses and has widest therapeutic window. It is eliminated via liver. Two long-term studies in healthy volunteers have demonstrated that fexofenadine, at doses upto 240 mg once daily for upto 12 months, is safe and well tolerated.[32] No dose-related increase in QT interval (QTc) were found with fexofenadine doses up to 800 mg once daily or 690 mg twice daily for 28 days.[33] Fexofenadine does not lead to sedation at therapeutic as well as supratherapeutic doses.

Limitations:

They do not influence the disease course.

Adverse effects:

- Sedation
- Mizolastine blocks HERG1 channels so cautious use is adviced with drugs that prolong Q-T interval. It may also cause electrolytic disturbance.

2nd LINE OF MANAGEMENT OF CHRONIC SPONTANEOUS URTICARIA:

Second generation anti histamines can be increased upto 4 times of their licenced dose[34]. This has been verified in studies using even up to fourfoldhigher than recommended doses of desloratadine,[35]fexofenadine,[36] levocetirizine[37]and rupatadine.[38]

SHORT COURSE OF CORTICOSTEROIDS:

Prednisolone has predominant glucocorticoid activity and is commonly used for longterm disease suppression. Oral corticosteroids i.e., prednisolone 0.5mg/kg/day is used for short period of 3-7 days to control severe attacks of urticaria and angioedema.[39] Prolonged use is avoided due to the risk of side effects.

3rd LINE OF MANAGEMENT OF CHRONIC SPONTANEOUS URTICARIA:

Montelukast:

It is a leukotriene receptor antagonist. It does not work in all types of urticaria. It works well for aspirin-sensitive urticaria.[40] A study found montelukast monotherapy ineffective in CSU when compared with cetirizine.[41]Dailydosage is 10 mg taken at bedtime. There are no important drug interactions.

Cyclosporine:

Cyclosporine is a powerful inhibitor of both cell mediated and humoral responses. It inhibits the release of histamine from basophils and tumor necrosis factor α production by mast cells[42]. There are many reports of efficacy of cyclosporine in urticaria.[43,44] Dosage of cyclosporine 3-5 mg/kg as a starting dose and tapered over three to four months. Onestudyshowed that prolonged treatment with cyclosporine is beneficial for maintaining remission in severe cases of chronic urticaria. Lowdose (2–3 mg/kg) therapy has also shown its beneficial effect in controlling urticaria.[45]Generally, the duration of cyclosporine therapy is 3 months. It spares the need for corticosteroids and is accompanied with mild side effects.[46]

Contraindications:

- Impaired kidney function
- Uncontrolled blood pressure
- Active serious infections
- Malignancy

Adverse effects:

- Renal dysfunction
- Hypertension
- Hyperkalemia
- Hyperuricemia

- Hypomagnesemia
- Hyperlipidemia

OMALIZUMAB:

Omalizumab is a humanized IgG1κ monoclonal antibody[47] manufactured by recombinant DNA technology in a Chinese hamster ovary mammalian cell line. It selectively binds to human IgE.

Humanization of murine anti-IgE was done to reduce the potential for human anti-mouse antibody response.

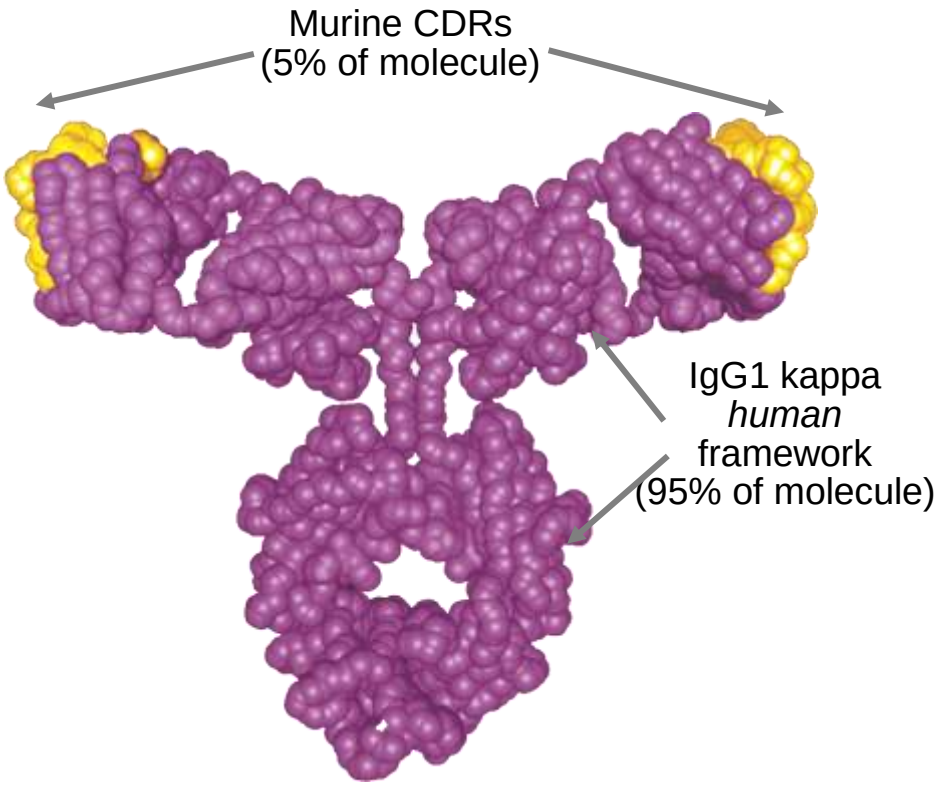


Fig: structure of omalizumab

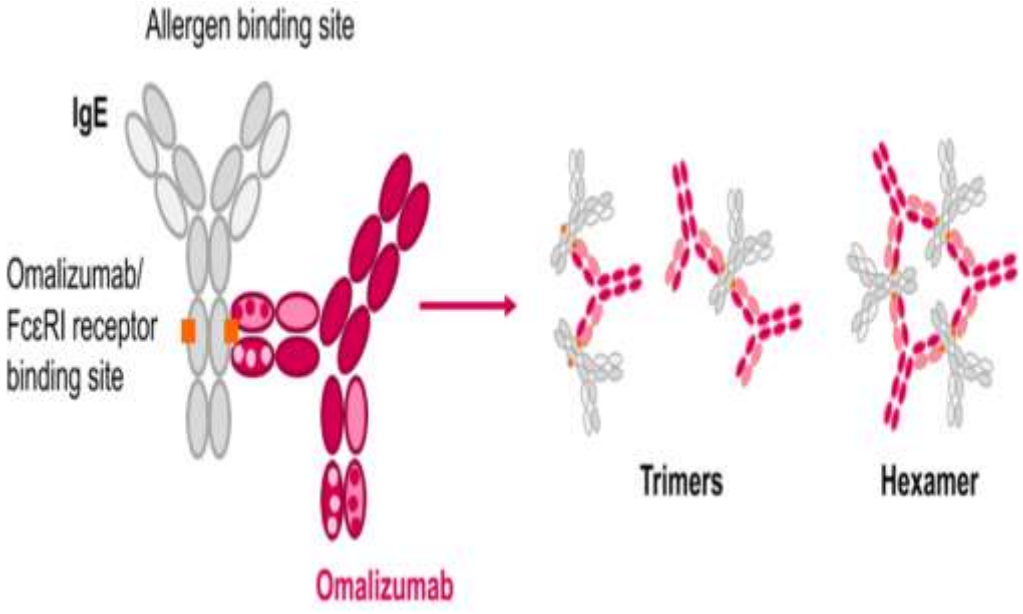


Fig: binding of Omalizumab to Cε3 domain of IgE

- Omalizumab binds to the Cε3 domain of IgE, forming trimers or hexamers[48,49] and preventing it from binding to FcεRI on the surface of mast cells and basophils
- Omalizumab cannot bind to receptor bound IgE.

INDICATIONS:

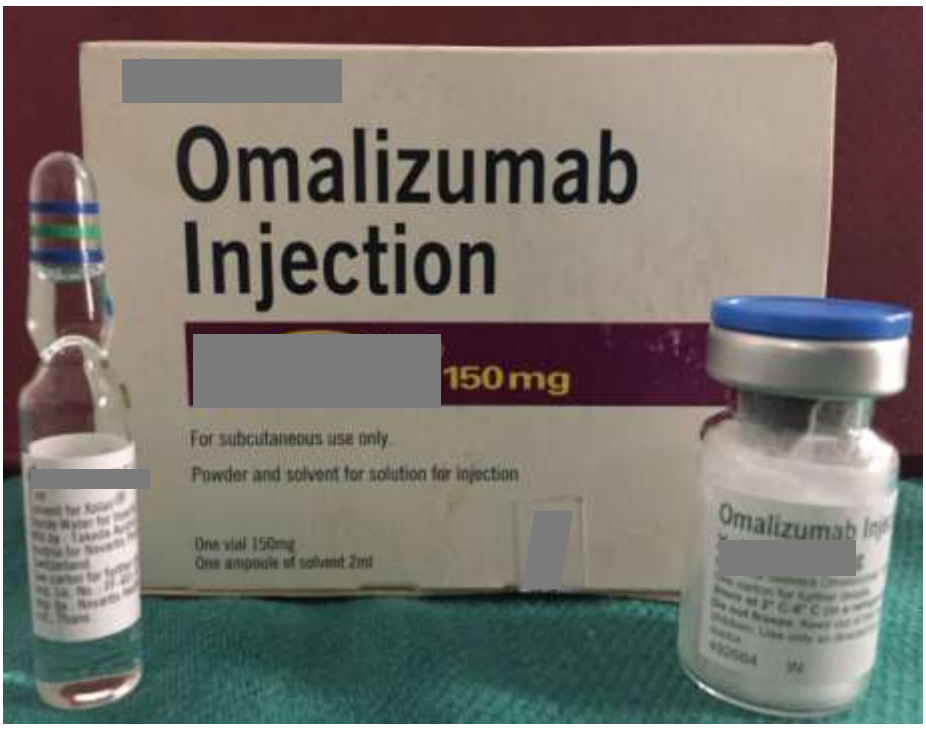
FDA approved indications:

- Chronic spontaneous urticaria refractory to standard 1st and 2nd line of management in patients of age more than 12 years.
- Allergic asthma

DOSE SCHEDULE:

Omalizumab is administered by subcutaneous route which either comes in prefilled syringe or with lyophilised formulation for reconstitution.

The approved dose is 300 mg (2 x 150mg once in 4 weeks).



SHELF LIFE:

4 years

PRECAUTIONS FOR STORAGE:

- It is stored in a refrigerator at 2-8°C. The drug should not be freezed.
- After reconstitution, omalizumab has to be used immediately. It should not be used after 8 hours at 2-8°C or 2 hours at 25°C.

MECHANISM OF ACTION:

The exact mechanism of action of omalizumab in chronic spontaneous urticaria is unknown.

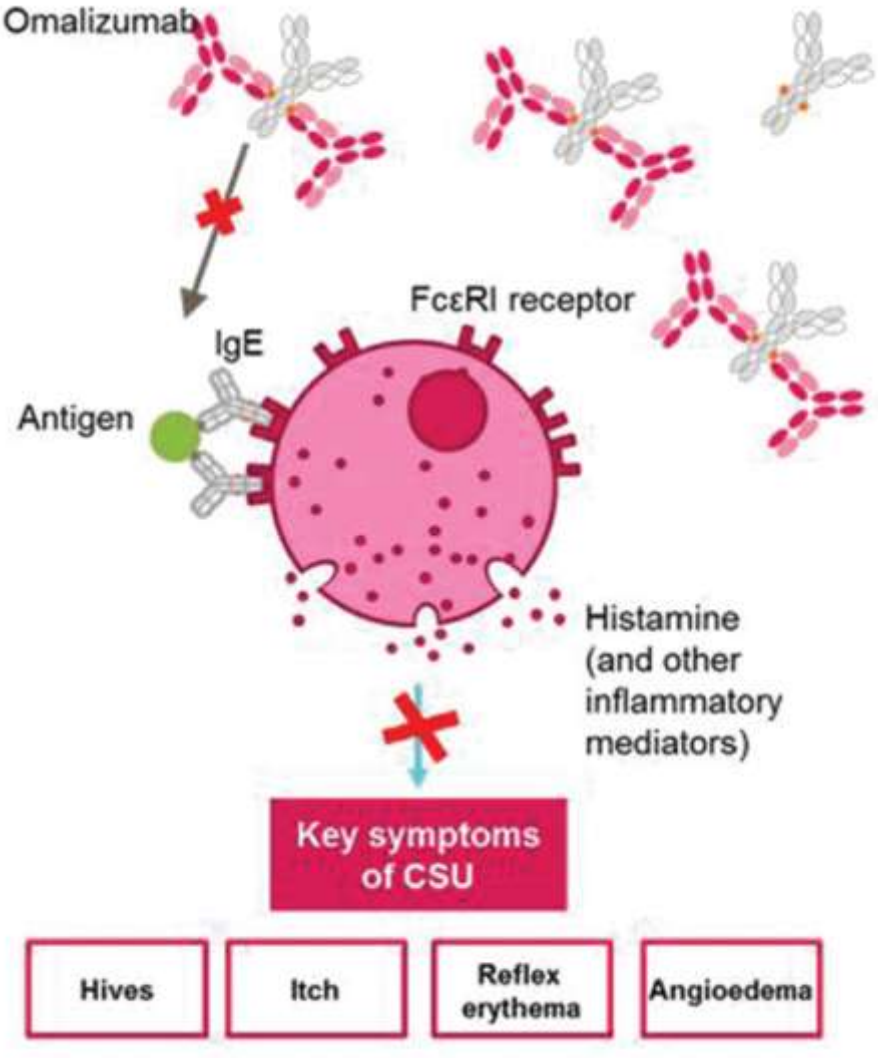


Fig: Mechanism of action of Omalizumab in CSU

One hypothesis for the mechanism of action of omalizumab in chronic spontaneous urticaria is that it lowers free IgE levels in the blood and subsequently in the skin. This leads to downregulation of surface IgE receptors,

thereby decreasing downstream signalling via the FcεRI pathway, resulting in suppressed cell activation and inflammatory responses. As a consequence, the frequency and severity of symptoms of chronic spontaneous urticaria are lessened.

Another hypothesis is that lowering circulating free IgE levels leads to a rapid and nonspecific desensitization of cutaneous mast cells. Downregulation of FcεRI may help to sustain the response.[50]

PHARMACOKINETIC PROPERTIES:

ABSORPTION:

After subcutaneous administration, the absolute bioavailability is 62%. It is absorbed slowly, reaches peak serum concentrations after an average of 6-8 days.

DISTRIBUTION:

In vitro omalizumab forms complexes of limited size with IgE. Based on population pharmacokinetics, the volume of distribution following subcutaneous administration is 78±32 ml/kg based on its lyophilised or liquid formulation.

ELIMINATION:

Clearance of omalizumab involves IgE clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Degradation occurs in the reticuloendothelial system and endothelial cells.

On population based pharmacokinetics, its serum eliminationhalf-life at steady state is about 24 days and apparent clearance at steady state for a patient of 80 kg weight was 3ml/kg/day.

CHARACTERISTICS IN PATIENT POPULATIONS:

No dose adjustments are necessary in patients with chronic spontaneous urticaria for

- Age (12-75 years)
- Race/Ethnicity
- Gender
- Body weight
- Body mass index,
- Baseline IgE
- Anti-FcεRI auto antibodies
- Renal impairment
- Hepatic impairment
- Concomitant use with H1 or H2 antihistamines and leukotriene antagonist.

CONTRAINDICATIONS:

- Hypersensitivity to active substance or any of its excipients
- Age less than 12 years

- It should not be used in pregnancy as it crosses placenta but its harm to foetus is unknown. (pregnancy category B).
- It should not be given during breast feeding as in non-human primates have shown excretion of omalizumab into milk.
- Parasitic(helminthic) infestations.

ADVERSE EFFECTS:[51,52]

- Sinusitis and upper respiratory tract infections
- Head ache
- Pyrexia
- Arthralgia
- Injection site reaction
- Anaphylaxis
- Arterial thromboembolic events
- Vasculitis and systemic eosinophilia in patients with Churgstrauss syndrome
- Idiopathic thrombocytopenia
- Increase in rate of helminthic infection

EFFECT OF OMALIZUMAB ON IgE:

In clinical studies of chronic spontaneous urticaria patients, omalizumab treatment led to a dose-dependent reduction of free IgE and an increase of total IgE levels in serum. Maximum suppression of free IgE was observed 3 days

after the first subcutaneous dose. After repeated dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab: IgE complexes which have a slower elimination rate compared with free IgE. After discontinuation of omalizumab, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16weekstreatment free followup period.[50]

STUDIES ON EFFICACY AND SAFETY OF OMALIZUMAB IN CHRONIC SPONTANEOUS URTICARIA (CSU):

There are three important landmark studies on the use of Omalizumab in chronic spontaneous urticaria.

First is a 24 weeks treatment with omalizumab 300 mg (n = 81), omalizumab 150 mg (n = 80), omalizumab 75 mg (n = 78), and placebo (n = 80) followedby a 16 weeks of followup in CSU management (ASTERIA I study).[53]

The second study was ASTERIA II study which was a 12week treatment with omalizumab 300 mg (n = 79), omalizumab 150 mg (n = 83), omalizumab 75 mg (n = 82), and placebo (n = 79) followed by 16 weeks followup,[54] and

The third study was GLACIAL study which was a global, multicentre, randomized, double blind, placebo controlled study of safety and efficacy of 24 weeks treatment with omalizumab 300 mg (n = 252) versus placebo (n = 84).[51]

In the above three studies, a total of 733 patients having CSU received omalizumab, and it was found to be effective and safe in the dose of 300 mg 4 weekly injections (subcutaneous). There was a 62–71% reduction in itch with omalizumab from baseline at 12 weeks, 34–44% of patients were itch free and hive free with omalizumab at 12 weeks, and 73–78% had improvement indermatology life quality index scores at 12 weeks, respectively. Common side effects observed were headache, joint pain, injection site reactions, and upper respiratory infections.

In 24 months followup study, of the 16 patients with severe CSU using fixed dose omalizumab (150 mg 2–4 weekly), 10 patients (62%) had remission after the first injection of omalizumab, and two patients discontinued therapy.[55] Of the 14 patients, four patients remained in remission for over 9 months after the last injection, and seven patients continued to be in remission with continuing maintenance therapy of antihistamines.

In another study presented in the annual conference of the American Academy of Allergy, Asthma, and Immunology (20–24 February2015) in Houston, Texas, 30 patients (15 male/15 female) with treatment resistant CSU being treated with omalizumab were followed for up to 4 years, with 15

patients completing 4 years treatment.[56] Complete remission was seen in 9/30 (30%) patientsafter the second dose, and there were significant improvements in UAS between pretreatment and first dose, with mean of 3.9, (95%confidence interval 3.45–4.3) which was maintained throughoutthe 4th year of therapy. Omalizumab was a safe and effectivealternative to corticosteroid for refractory urticaria patients. It isequally effective and safe for long term use up to 4 years.

Although there are no reports of comparative studies of omalizumab in Indian patients, there are two reports published earlier. First is a single case study of 45year old female who presented with severe CSU since 10 years of age not responding to antihistamines and steroids.[57] The patient was treated with cyclosporine for sarcoidosis and incidentally her urticaria responded to cyclosporine. Considering the autoimmune aetiology for CSU, omalizumab was administered to this patient and the patient's response for CSU was dramatic.

The second report is a case study of omalizumab in five patients with CSU.[58] These five patients had severe urticaria that required multiple antihistamines, steroids, or dapsone to control symptoms and in spite of therapy, they had severe symptoms. In the absence of recommended dose for omalizumab in CSU, the patients were treated with omalizumab according to the dose schedule of asthma. There was a significant improvement in all the patients, with reduction in UAS7 and need of antihistamines. At the end of 4 months, two patients were free from symptoms and the other three required

only antihistamines to control their symptoms. Side effects were recorded in two patients in the form of headache and fatigue.

THE USE OF OMALIZUMAB IN CHRONIC SPONTANEOUS URTICARIA IN INDIA[59]

The following recommendations were issued on the use of omalizumab for treatment of chronic spontaneous urticaria in India:

- Omalizumab is approved in adults and adolescents ≥12 years of age with chronic spontaneous urticaria refractory to standard of care by the Health authority of India.
- Assessment of the severity of chronic spontaneous urticaria to be done using UAS7 score.
- Serum IgE measurement is not needed before the start of omalizumab therapy for chronic spontaneous urticaria.
- It is recommended as the third line therapy for management of chronic spontaneous urticaria by EAACI/GA2LEN/EDF/WAO 2013 guidelines.
- Omalizumab should only be administered in a setting where the appropriate medications and equipment are available to respond to an episode of anaphylaxis.
- Recommended dose and best response are seen with 300 mg subcutaneous injection once in 4 weeks. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer.

- Body weight measurement is not required for calculating the dose of omalizumab.
- Ice compress may be applied at site of injection to minimize local reactions.
- All patients administered omalizumab to be observed for 2 hrs after dosage for any allergic reactions.
- Dose of omalizumab in patients with hepatic/renal compromised status may remain same (i.e., 300 mg once every 4 weeks).
- Omalizumab should only be used during pregnancy if clearly needed.
- Caution should be exercised when administering omalizumab to a nursing woman.

SPECIAL PRECAUTIONS ADMINISTRATION AND DISPOSAL:

For subcutaneous administration Inj omalizumab 150mg,

- 1.2 ml of the diluent is drawn into a syringe with a large bore 18 gauge needle.
- The vial is placed upright on a flat surface, the needle is inserted and the diluent is transferred to the vials containing the lyophilised powder under aseptic techniques.
- The vial is kept in an upright position, vigorously swirled (not to be shaked) for approximately 1 minute to evenly wet the powder. The vial

has to been swirled 5-10 seconds approximately every 5 minutes so that the powder gets dissolved.

- The reconstituted injection appears as clear to slightly opalescent, colourless to pale brownishyellow.
- The vial is inverted for atleast 15 seconds in order to allow the solution to drain towards the stopper.
- A new 2ml syringe is used to draw the reconstituted solution from the vial. The air and large bubbles are expelled.
- After reconstitution, omalizumab has to be used immediately. It should not be used after 8 hours at 2-8°C or 2 hours at 25°C.
- The injection is administered in the deltoid region of the arm or the thigh.
- The patient has to be monitored for vitals and any adverse effects.

MATERIALS AND METHODS

STUDY DESIGN:

Non probability - convenience sampling

Prospective Study

STUDY POPULATION:

Sample size -30

STUDY DURATION:

1 year

PLACE OF STUDY:

Department of Dermatology

Govt. Stanley Medical College

INCLUSION CRITERIA:

- Both sex
- Age >12 years
- Patients refractory to updosing of antihistamines.
- Patients willing for informed consent
- Patients willing for follow up

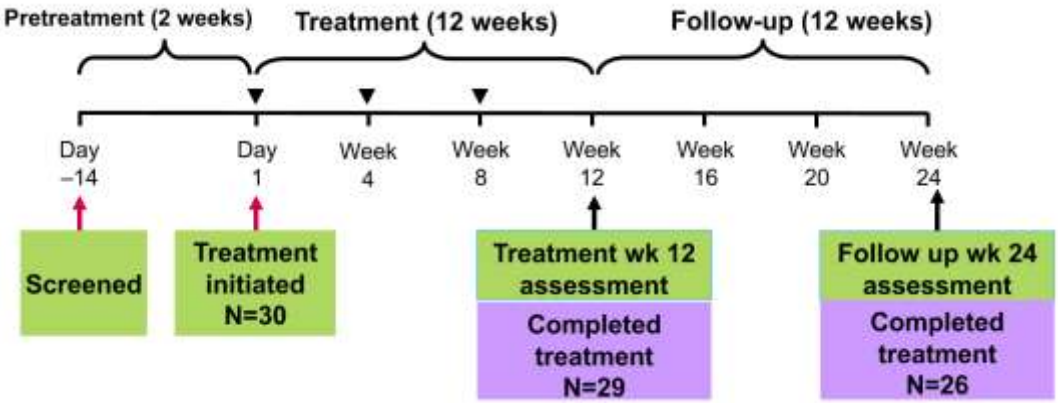
EXCLUSION CRITERIA:

- Hypersensitivity to drug
- Pregnancy
- Lactation
- Parasitic infestations
- Tuberculosis/HIV/Hepatitis

SCREENING VISIT:

Thorough history of the patients was taken. Patients were assessed and selected based on the inclusion and exclusion criteria. Written informed consent was obtained. Clinical assessment of the condition was carried out.

STUDY PLAN:



The patients who fulfilled the inclusion criteria and willing to take part in the study were screened. After obtaining informed written consent, therewere admitted in our Dermatology ward and administered Inj Omalizumab 300mg subcutaneously. Patients were monitored for vitals and any adverse reactions. Patients were advised to maintain urticaria activity score7(UAS7) and reviewed weekly as outpatient. The patient was advised to come for next 2 doses of Inj Omalizumab 300mg every 4 weeks and followed up for next 12 weeks. The safety and effectiveness was studied by using urticarial activity score7(UAS7).

INVESTIGATIONS:

The following investigations were done at the start of the study (screening visit)

- Blood haemoglobin
- Platelet count
- Total count
- Differential blood count
- Erythrocyte sedimentation rate
- Absolute eosinophil count
- Serum IgE levels.
- Liver function test
- Renal function test
- Anti nuclear antibody
- C-reactive protein
- ELISA for HIV
- RPR for syphilis
- HBsAg
- Anti HCV
- Chest X-ray and Mantoux test
- ECG and Echocardiograph
- Stool for ova and cyst
- Thyroid profile

- Autologous serum skin test

MONITORING PARAMETER:

- Patients were monitored every week clinically with URTICARIA ACTIVITY SCORE 7
- Adverse events were analysed at each follow up visit.
- Patient compliance was confirmed at every follow up visit.

CLINICAL EFFECTIVENESS ASSESSMENT BY PATIENTS USING URTICARIA ACTIVITY SCORE 7.

At each of the visits, clinical effectiveness was assessed as follows:

Week No:

Day	Itch severity score	Wheals score
Day 1		
Day 2		
Day 3		
Day 4		
Day 5		
Day 6		
Day 7		

The urticaria activity score7 was analysed during treatment period of 12 weeks and during the follow up period of another 12 weeks.

OBSERVATION AND RESULTS

Statistical methods are extensively used in modern medical research. Statistical methods like, descriptive statistics, correlation analysis, t-test, chi-square test, ANOVA have become some of the most common applications of statistical methods in medical research.

AGE-WISE DISTRIBUTION:

Age wise distribution of study population

Age		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	< 20 Years	2	6.7	6.7	6.7
	20 - 40 Years	17	56.7	56.7	63.3
	> 41 years	11	36.7	36.7	100.0
	Total	30	100.0	100.0	

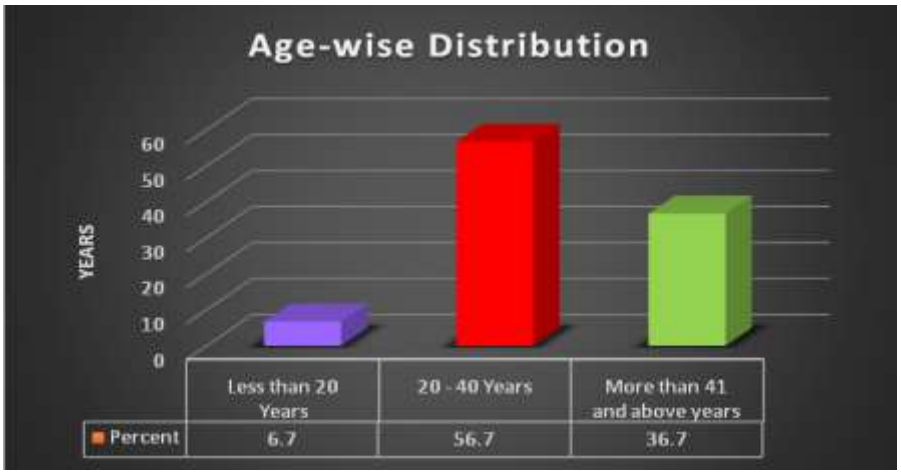


Fig: Age-wise distribution of study population

In this study the 56.7% are between 20 – 40 years of age, followed by 36.7% are more than 41 years of age.

SEXWISE DISTRIBUTION OF PATIENTS

Sex	No of patients	Percent	Valid Percent	Cumulative Percent
Male	7	23.3	23.3	23.3
Female	23	76.7	76.7	100.0
Total	30	100.0	100.0	

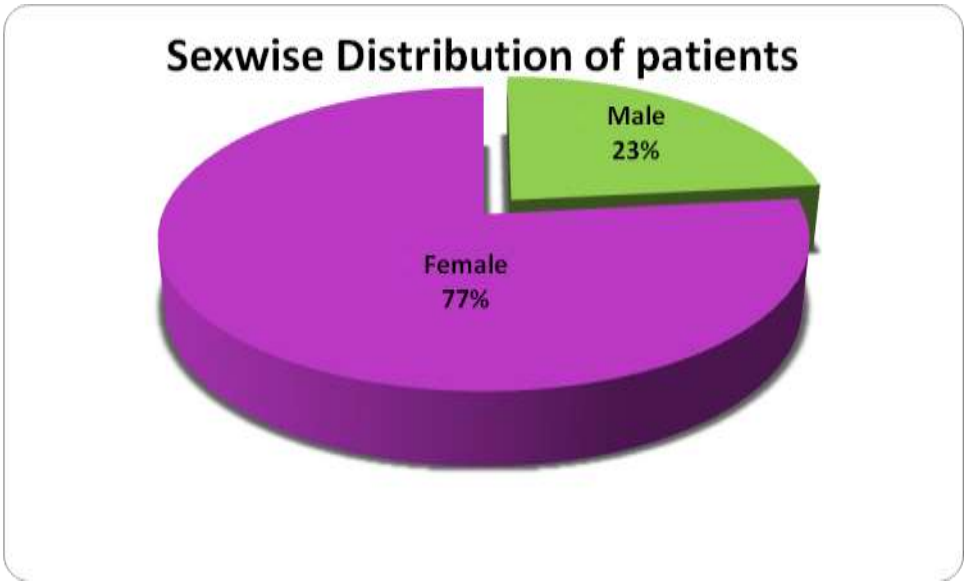


Fig: Sexwise distribution of study population

Females constituted 77% and males 23% of study population.

PRETREATMENT CLASSIFICATION OF CSU:

Pre Treatment Category

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Mild CSU	3	10.0	10.0	10.0
	Moderate CSU	15	50.0	50.0	60.0
	Severe CSU	12	40.0	40.0	100.0
	Total	30	100.0	100.0	

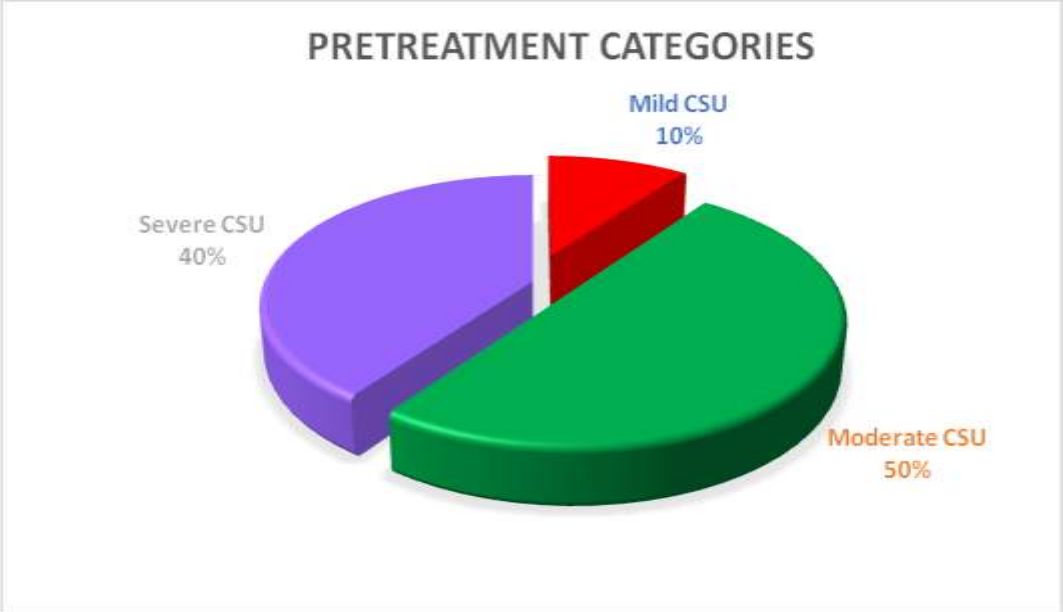


Fig: Pretreatment classification of CSU

90% of the pretreatment study population are under the category of moderate to severe CSU.

OCCUPATION WISE DISTRIBUTION OF STUDY POPULATION:

Table: Occupation wise distribution

Occupation	Frequency	Percent	Valid Percent	Cumulative Percent
BUSINESS	2	6.7	6.7	6.7
COOLIE	4	13.3	13.3	20.0
HOUSE KEEPER	1	3.3	3.3	23.3
HOUSE WIFE	13	43.3	43.3	66.7
OFFICE ASST	2	6.7	6.7	73.3
PLUMBER	1	3.3	3.3	76.7
STUDENT	4	13.3	13.3	90.0
TEACHER	3	10.0	10.0	100.0
Total	30	100.0	100.0	

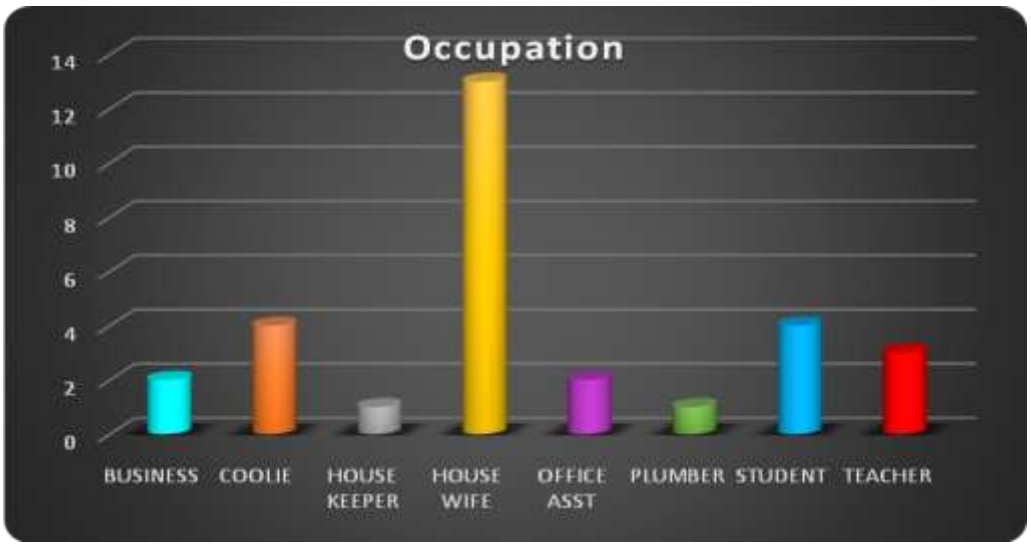


Fig: Occupation wise distribution of study population

Out of the several occupational groups, Housewives wife consisted 43% of the study population. It was inferred that the urticarial was troublesome in doing day to day household activities and so a large no of patients reported the Dermatology OPD.

PREVALENCE OF URTICARIA IN STUDY POPULATION:

Table: Prevalence of urticaria in years

No of years of urticaria	No of people	Percent	Valid Percent	Cumulative Percent
1	3	10.0	10.0	10.0
2	6	20.0	20.0	30.0
3	3	10.0	10.0	40.0
4	1	3.3	3.3	43.3
4	3	10.0	10.0	53.3
5	1	3.3	3.3	56.7
6	3	10.0	10.0	66.7
7	2	6.7	6.7	73.3
8	2	6.7	6.7	80.0
9	1	3.3	3.3	83.3
12	1	3.3	3.3	86.7
13	1	3.3	3.3	90.0
14	1	3.3	3.3	93.3
19	1	3.3	3.3	96.7
20	1	3.3	3.3	100.0
Total	30	100.0	100.0	

This table show the highest prevalence of urticariain years in this study population is 20 years.

OCCURRENCE OF CSU – DAYS/WEEK:

Table: Occurrence of urticaria per week

Days/week urticarial present	No of patients	Percent	Valid Percent	Cumulative Percent
2	1	3.3	3.3	3.3
3	3	10.0	10.0	13.3
4	5	16.7	16.7	30.0
5	9	30.0	30.0	60.0
6	6	20.0	20.0	80.0
7	6	20.0	20.0	100.0
Total	30	100.0	100.0	

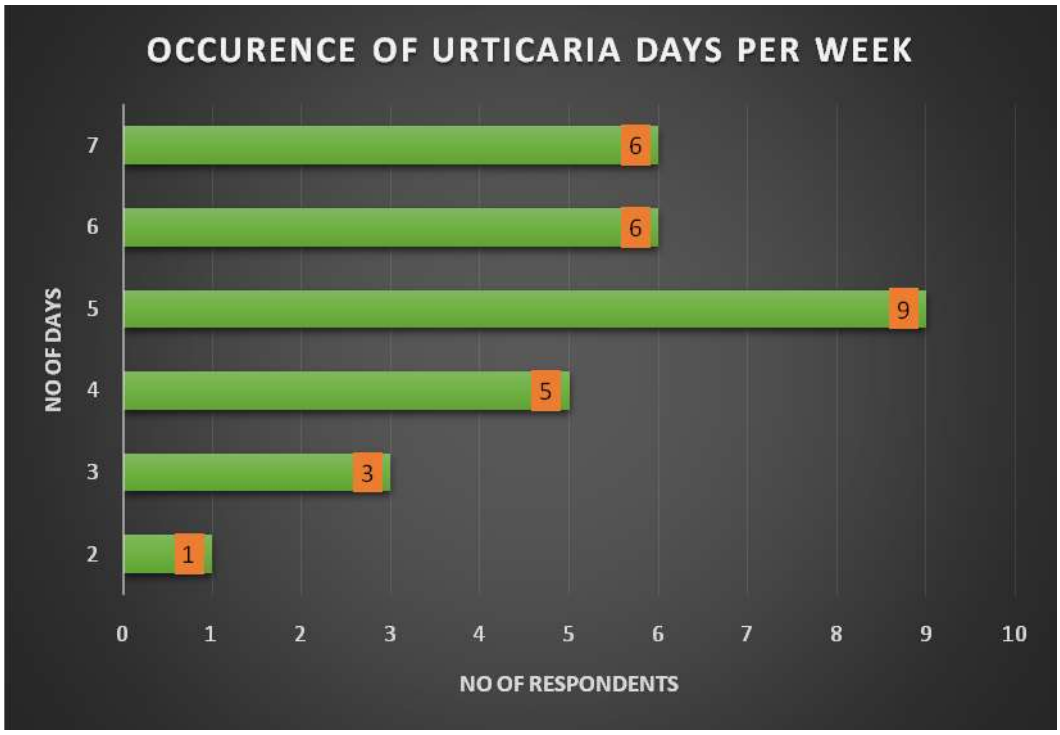


Fig: Occurrence of urticaria - days/week.

Most of the study population (21 pts) had incidence of urticarial lesions more than 5 days per week.

TOTAL NUMBER OF URTICARIAL LESIONS PER DAY:

Table: Total number of urticarial lesions per day

Number of urticarial lesions	No of patients	Percent	Valid Percent	Cumulative Percent
10	1	3.3	3.3	3.3
20	3	10.0	10.0	13.3
25	5	16.7	16.7	30.0
30	3	10.0	10.0	40.0
35	2	6.7	6.7	46.7
40	4	13.3	13.3	60.0
50	7	23.3	23.3	83.3
60	2	6.7	6.7	90.0
70	2	6.7	6.7	96.7
80	1	3.3	3.3	100.0
Total	30	100.0	100.0	

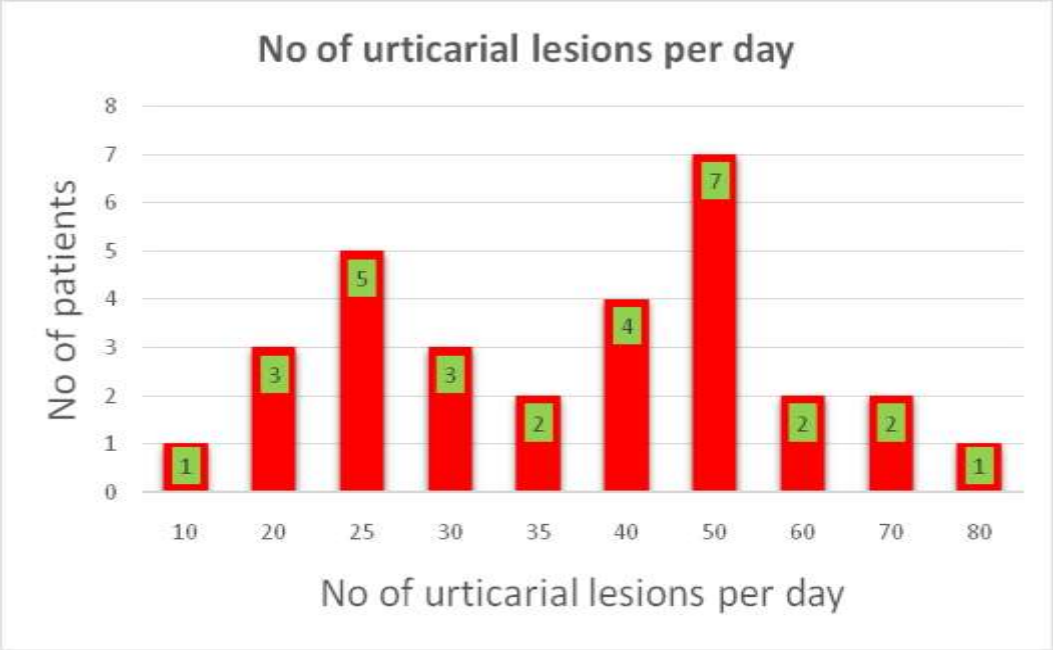


Fig: Number of urticarial lesions per day in the study population

40% of the study population had more than 50 wheals per day. This prevented them to do their day to day activities effectively.

ANGIOEDEMA IN THE STUDY POPULATION:

Table: Angioedema

Angioedema	No of patients	Percent	Valid Percent	Cumulative Percent
NO	27	90.0	90.0	90.0
YES	3	10.0	10.0	100.0
Total	30	100.0	100.0	

Only 10% of the study population had angioedema.

ASST POSITIVITY IN THE STUDY POPULATION:

Table: ASST positivity

ASST Result		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negative	28	93.3	93.3	93.3
	Positive	2	6.7	6.7	100.0
	Total	30	100.0	100.0	

Only 6.7% of the study population were ASST positive i.e., they had auto immune urticaria.

ABSOLUTE EOSINOPHIL COUNT IN THE STUDY POPULATION:

Table: Absolute eosinophil count

AEC	No of patients	Percent	Valid Percent	Cumulative Percent
Normal level	25	83.3	83.3	83.3
Increased	5	16.7	16.7	100.0
Total	30	100.0	100.0	

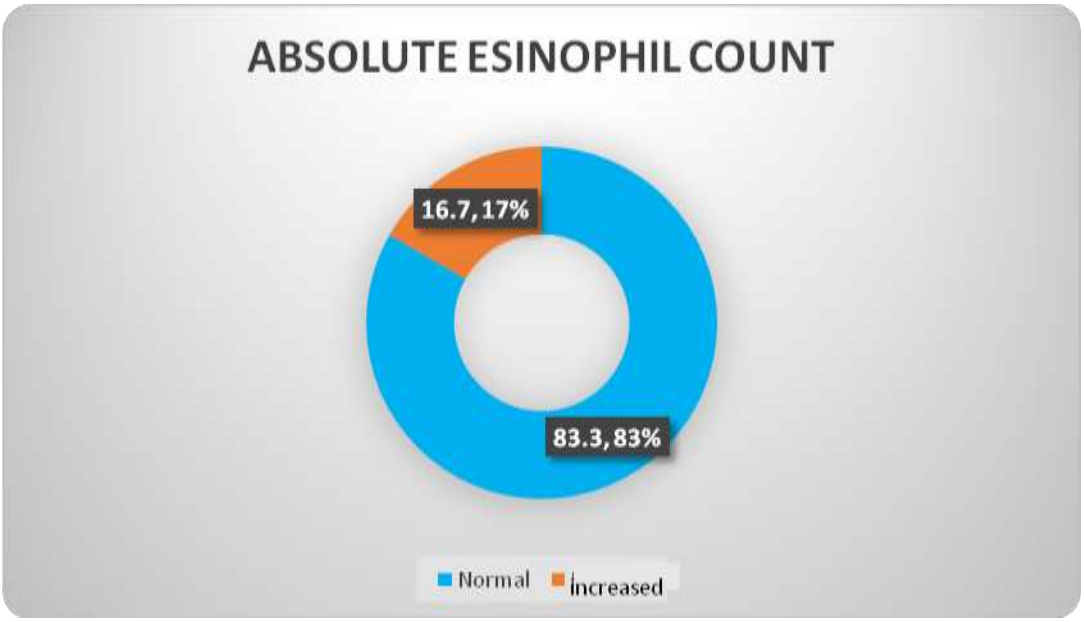


Fig: Absolute eosinophil levels in study population

83% of the study population had normal eosinophil count.

SERUM IgE LEVELS IN THE STUDY POPULATION:

Table: Serum IgE levels

Serum IgE levels	Frequency	Percent	Valid Percent	Cumulative Percent
Normal	11	36.7	36.7	36.7
Increased	19	63.3	63.3	100.0
Total	30	100.0	100.0	

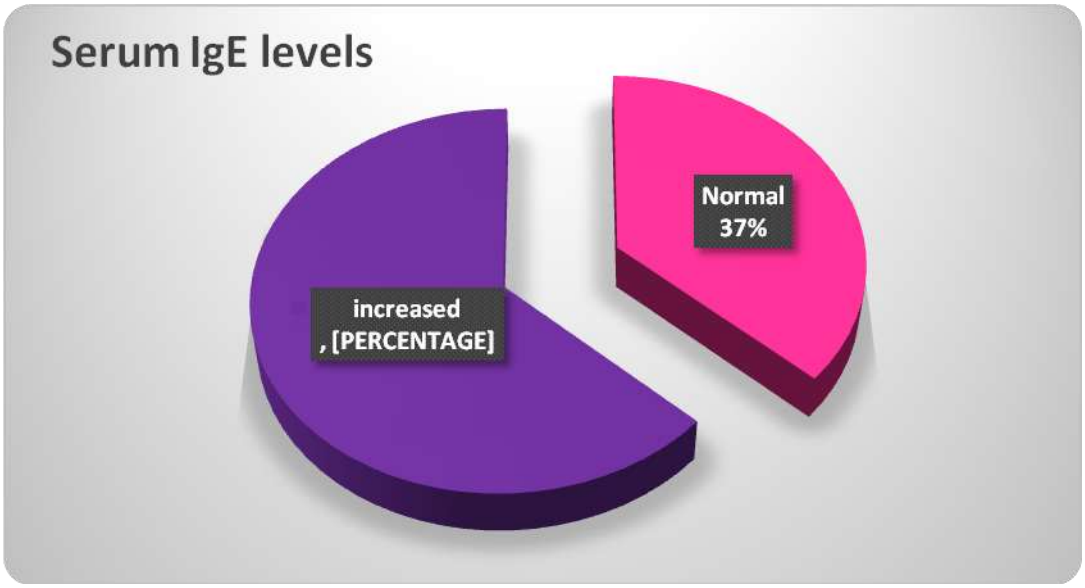


Fig: Serum IgE levels of the study population

63% of the study population had increased serum IgE levels.

II. Categorical data analysis:

Qualitative or categorical data are frequently collected in medical investigation. The qualitative variables include Sex, blood groups, Attacked or not attacked as well as the grouped quantitative variables such as in control, mild, severe.

When the interest lies in the association between two qualitative variables, then the frequencies can be presented in a two-way table or cross table.

Cross tabulation and Chi square analysis:

RELATION SHIP OF ANGIOEDEMA, AEC AND SERUM IgE LEVELS WITH SEX:

Sex Vs Angioedema

			Angioedema		Total
			No	Yes	
Sex	Male	Count	6	1	7
		%	85.7%	14.3%	100.0%
	Female	Count	21	2	23
		%	91.3%	8.7%	100.0%
Total		Count	27	3	30
		% within SexCode	90.0%	10.0%	100.0%

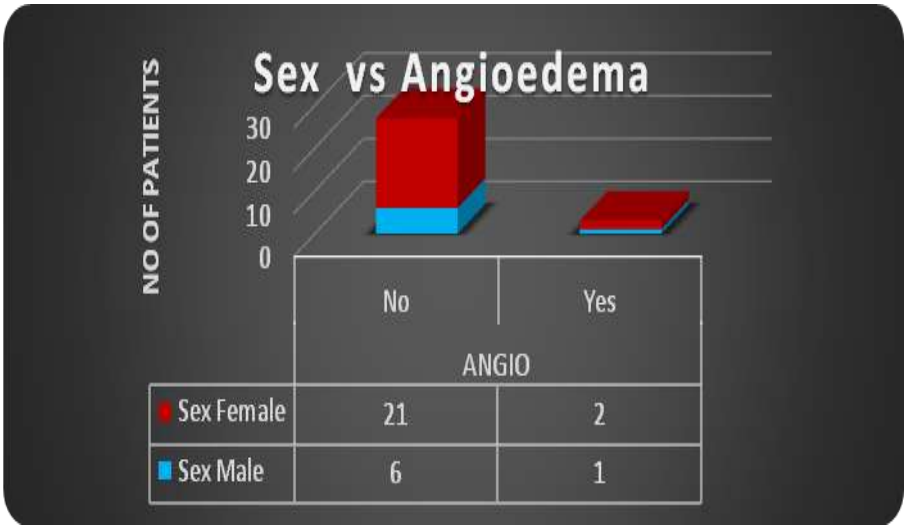


Fig: sex vs angioedema in the study population

Sex Vs Absolute eosinophil count

			AEC		Total
			Normal	increased	
Sex	Male	Count	7	0	7
		%	100.0%	0.0%	100.0%
	Female	Count	18	5	23
		%	78.3%	21.7%	100.0%
Total		Count	25	5	30
		% within SexCode	83.3%	16.7%	100.0%

Sex Vs Serum IgE levels

			Serum IgE levels		Total
			Normal	Increased	
Sex Code	Male	Count	2	5	7
		% within SexCode	28.6%	71.4%	100.0%
	Female	Count	9	14	23
		% within SexCode	39.1%	60.9%	100.0%
Total		Count	11	19	30
		% within SexCode	36.7%	63.3%	100.0%

b). CHI-SQUARE TEST FOR ASSOCIATION

When the interest is to determine whether the proportion of improvement or success rate in one group (say treatment group) differs significantly from a control group. The most commonly used statistical method is the Chi-Square test. This test is used to test whether there is any association between the two groups or the success rate in treated group differs from a control group. The Chi square test compares the difference between the observed counts and the expected counts in a contingency table. If the differences are large, then the two variables under the investigation ae likely to be associated with each other**.**

Using Chi square the relationship between sex and angioedema, AEC and serum IgE were analysed. Chi square revealed that the angioedema, Absolute eosinophil count and serum IgE are not related to sex.

III.Correlation Analysis:

One of the common objectives of the study is to investigate the relationship between two characteristics of a population. The correlation coefficient can be used to test whether there is any linear relation between the variables in the population. The t statistic can be used to test the null hypothesis that the population correlation coefficient is 0.

CORRELATION BETWEEN OCCURRENCE OF URTICARIA PER WEEK, NUMBER OF YEARS AND NUMBER OF LESIONS PER DAY:

		Occurrence of urticariaper week	Number of years	Number of lesions per day
Occurrence of urticaria per week	Pearson Correlation	1	.120	.015
	Sig. (2-tailed)		.526	.936
	N	30	30	30
Number of years	Pearson Correlation	**.120**	1	.012
	Sig. (2-tailed)	.526		.950
	N	30	30	30
Number of lesions per day	Pearson Correlation	.015	.012	1
	Sig. (2-tailed)	.936	.950	
	N	30	30	30

Number of Urticarial lesions per day and its occurrence per week are uncorrelated, r (30) = .015, p= .936

Number of years andoccurrence of Urticariaper week are uncorrelated, r (30) = .120, p = .526,

Number of years and Number of urticarial lesions per day uncorrelated, r (30) = .012, p = .950,

The three variables Number of years, Occurrence of urticaria per week and Number of urticarial lesions per day are not linearly correlated.

IV. TESTING OF HYPOTHESES

The statistical frame work employs probability distributions to evaluate how close is the proposed hypothesis to the sample and hence the population from which is drawn. **All tests in this study are tested at Level of significance α = 5% (= .05)**

a). Independent samples T-Test

Very often, in medical research, a researcher encounters the problem of comparing two groups on a continuous outcome. This is to test whether on an average, one group is significantly higher or lower than the other. Here the two groups are male and female and the continuous outcomes are 1. Number of years, 2. Occurrence of utricaria per week and Number of lesions.

INFLUENCE OF SEX ON NUMBER OF YEARS, OCCURRENCE OF URTICARIA PER WEEK AND NUMBER OF LESIONS:

	Sex Code	N	Mean	Std. Deviation	Std. Error Mean
Number of years	Male	7	6.14	4.337	1.639
	Female	23	5.93	5.382	1.122
Occurrence of urticaria per week	Male	7	5.14	1.069	.404
	Female	23	5.14	1.459	.304
Number of lesions	Male	7	37.86	9.940	3.757
	Female	23	40.87	18.869	3.934

1). Male (M = 6.14, S.D = 4.33) and female (M = 5.93, S.D = 5.38) did not differ significantly on Number of years , t (28) = .093, p = .926.

2). Male (M = 5.14, S.D = 1.07) and female (M = 5.14, S.D = 1.46) did not differ significantly on Occurrence of urticaria per week, t (28) = ..01, p = .999.

3). Male (M = 37.86, S.D = 9.94) and female (M = 40.87, S.D = 18.87) did not differ significantly on Number of urticarial lesions , t (28) = ..402, p = .691

Inference: In the study based on Independent Sample T test, the sex had no influence on (1) Number of years, (2) Occurrence of urticarial per week and (3) Number of urticarial lesions.

b) Oneway ANOVA

three categories of age(less than 20 years, between 21 and 40 years and more than 41 years) were considered and testedwhether the mean Numbers of

years, mean AEC and mean Serum IgE level differs among the three categories of age.

The test is done under the null hypothesis H_0 that the mean Numbers of years, mean AEC and mean Serum IgE level do not differ significantly due to age is tested against the alternative hypothesis that at least one age group is different from other age groups.

INFLUENCE OF AGE OVER NUMBER OF YEARS, AEC & SERUM IgE:

		Sum of Squares	df	Mean Square	F	Sig.
Number of years	Between Groups	364.608	2	182.304	.607	.552
	Within Groups	8109.559	27	300.354		
	Total	8474.167	29			
AEC	Between Groups	62121.722	2	31060.861	1.504	.240
	Within Groups	557737.078	27	20656.929		
	Total	619858.800	29			
Serum IgE Levels	Between Groups	187609.504	2	93804.752	1.808	.183
	Within Groups	1400709.424	27	51878.127		
	Total	1588318.928	29			

From one-way ANOVA the inference of this study is, the number of years, AEC and serum IgE levels did not differ due to the age.

c) Paired t tests:

The context of paired samples arises in studies comparing the difference in outcomes before and after an intervention and twin studies where the

measurement on one entity is related to the measurement on the other and thus, the observations are dependent. When the outcomes are continuous in nature, the means are compared using a paired samples test such as paired t test.

In this study the null Hypothesis H_0, that the treatment is ineffective, is tested against the alternative hypothesis H_1 , namely the treatment is effective, over different periods of study

(i) Paired t test 1 Effectiveness of intervention during treatment period):

Paired Samples Statistics – treatment period

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PreTreatWK1	26.59	29	8.305	1.542
	TreatWK12	5.4138	29	3.56087	.66124

Paired Samples Correlations –treatment period

		N	Correlation	Sig.
Pair 1	PreTreatWK1 & TreatWK12	29	.560	.002

Paired Samples Test –treatment period

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PreTreatWK1 - TreatWK12	21.17241	6.96455	1.29328	18.52324	23.82159	16.371	28	.000

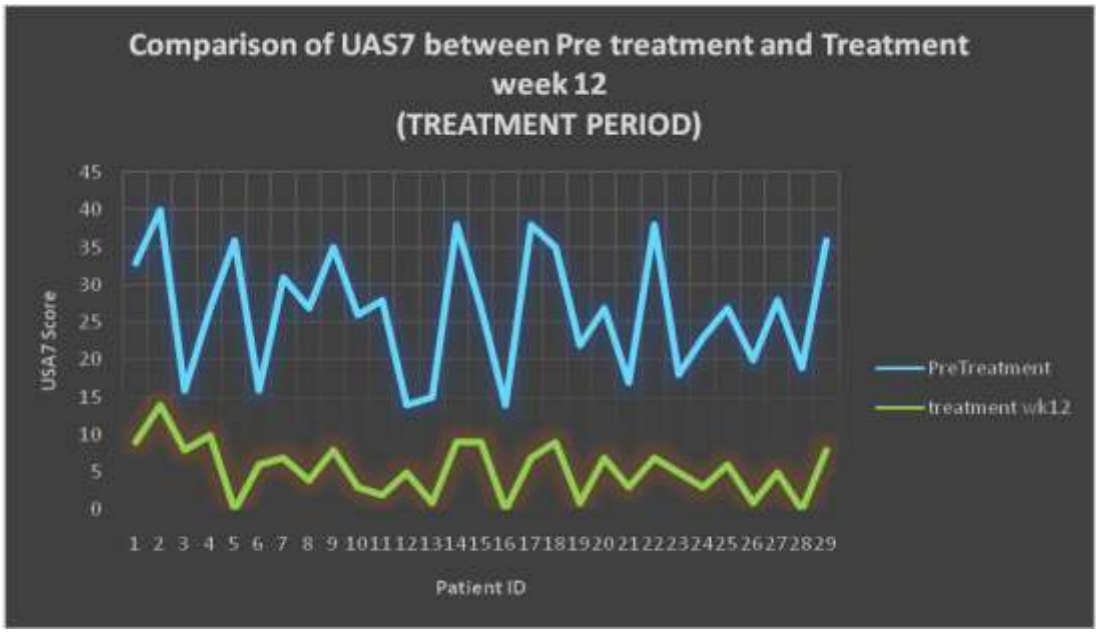


Fig: comparison of UAS7 during treatment period

A paired sample t test indicated that scores were significantly higher for PreTreatWK1 (M = 26.59, S.D = 8.31) than for TreatWK12 ((M = 26.59, S.D = 8.31) , t (28)= 16.37 , p< .001

Inj omalizumab had rapid and sustained improvement in the reduction of UAS7 score during the treatment period.

Paired t- Test 2 (Effectiveness during follow-up period)

Paired Samples Statistics –follow up period

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	TreatWK12	4.9615	26	3.28001	.64326
	Follow up WK24	5.1538	26	4.16358	.81654

Paired Samples Correlations –follow up period

		N	Correlation	Sig.
Pair 1	TreatWK12 & followup WK24	26	.692	.000

Paired Samples Test – follow up period

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	TreatWK12 - Follow upWK24	-.19231	3.03340	.59490	-1.41753	1.03291	-.323	25	.749

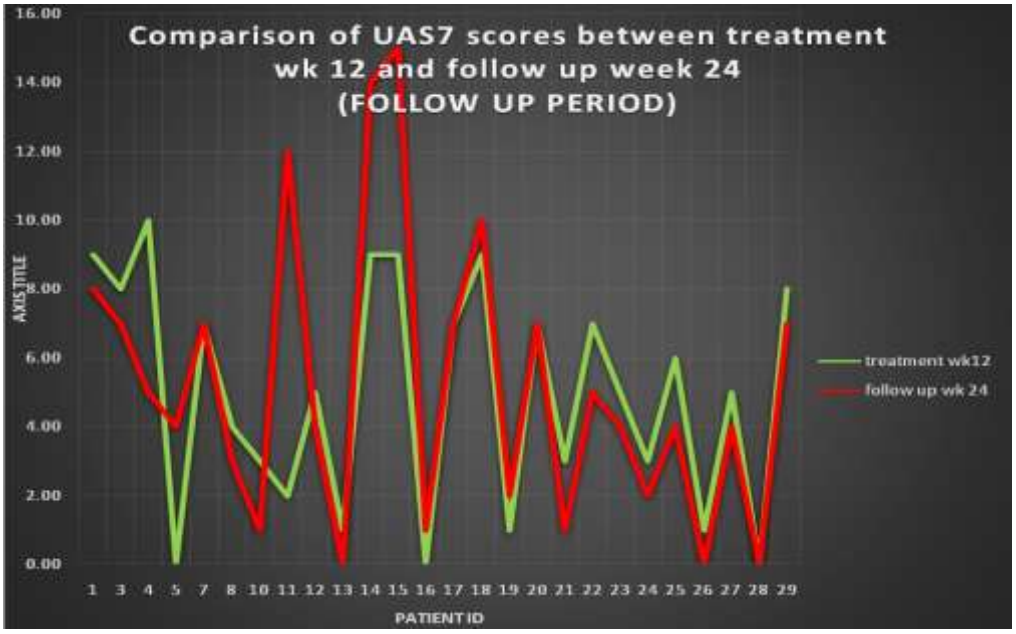


Fig: comparison of UAS7 during follow up period

A paired sample t test indicated that scores were not significantly differ for Treat WK12 - (M = 26.15, S.D = 26.15) and for follow upWK24 ((M = 5.1538, S.D = 4.16358) , t (25)= .323 , p= .749

In the analysis it was found that there is no significant reduction in the UAS7 score from the treatment week12 to follow up week 24.

(iii) Paired T-Test (Entire study period)

Paired Samples Statistics – Entire study period

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PreTreatWK1	26.15	26	26.15	1.551
	FollowupWK24	5.1538	26	4.16358	.81654

Paired Samples Correlations –Entire study period

		N	Correlation	Sig.
Pair 1	PreTreatWK1 &followupWK24	26	.563	.003

Paired Samples Test – Entire study period

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PreTreatWK1 – follow up WK24	21.00000	6.54217	1.28303	18.35756	23.64244	16.368	25	.000

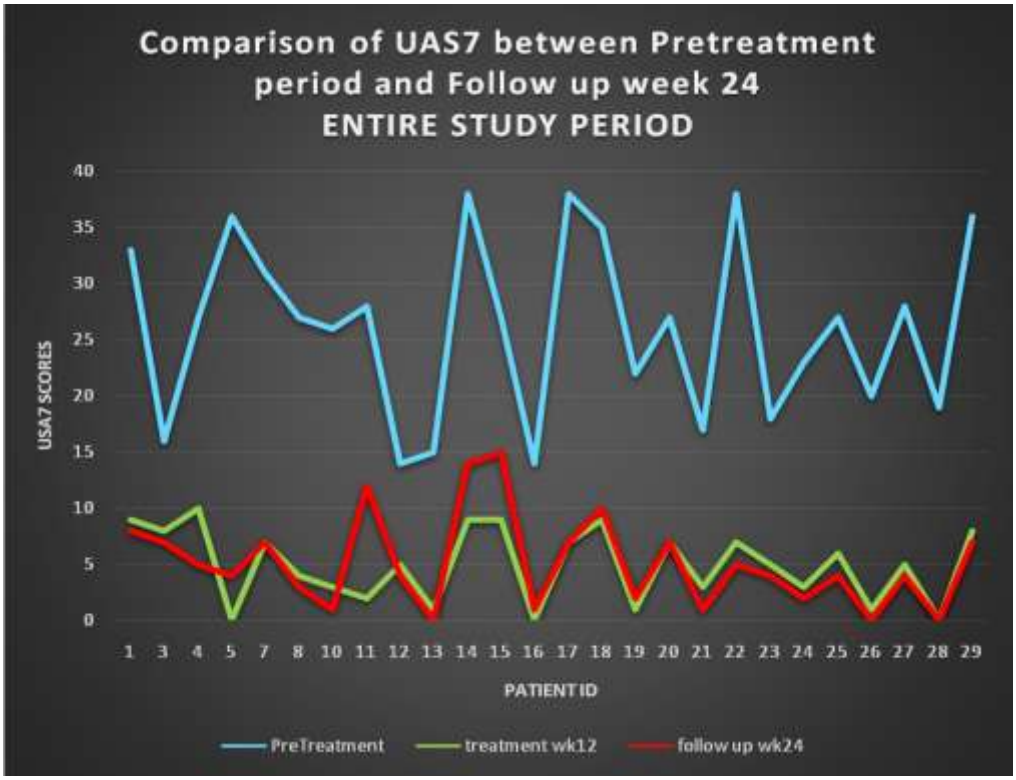


Fig: comparison of UAS7 entire study period

Pt 2,6 and 9 lost follow up.

A paired sample t test indicated that scores were significantly higher forPreTreatWK1 (M = 26.15, S.D = 26.15) than for Follow up WK24 ((M = 5.1538, S.D = 4.16358) , t (28)= 16.37 , p< .001

From paired t test, InjOmalizumabwas effective in drastically reducing the UAS7 from pretreatment period to treatment week12 and their effectiveness was good, but from Treatment week 12 to follow up week 24, the effectiveness of Omalizumabwasnot significant. After the treatment period, there was no significant improvement. Overall the effectiveness of omalizumab in this study population varied between patients.

SUMMARIZING STUDY DATA

The more commonly used summary measures are 1. Arithmetic mean or mean and 2. Standard deviation. While mean will do the role of a representative (location of a central value), the standard deviation will tell the closeness of the to the central value.

Descriptive measures on USA7 scores during the study period

	Pre treat	Treat WK4	Treat WK8	Treat WK12	Follow up Wk16	Follow up Wk20	Follow up Wk24
Mean	26.40	7.97	6.10	5.41	4.79	5.48	5.15
Standard Deviation	8.22	4.74	4.08	3.56	3.18	4.04	4.16
Number	30	30	29	29	29	27	26

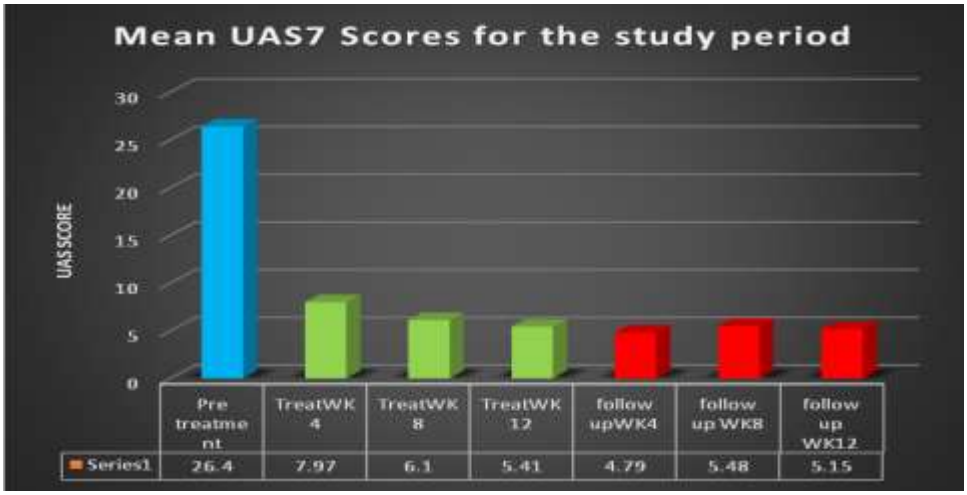


Fig: Mean UAS7 for the entire study period

There is a rapid and sustained improvement in the mean UAS7 during the treatment period and there is a slight surge in the mean UAS7 in the follow up period**.**

Gantt chart

A Gantt chart is a type of bar chart that illustrates a project schedule. Gantt charts illustrate the start and finish dates of the terminal elements and summary elements of a project. Terminal elements and summary elements comprise the work breakdown structure of the project. Modern Gantt charts also show the dependency (i.e., precedence network) relationships between activities.

Transition to lower level (cure) during the study period. Gantt chart

Categorization	Pre	T4	T8	T12	PoT4	PoT8	PoT12
Severe (28 – 42)	**12**						
Moderate (16- 27)	**15**	**1**					
Mild (7 – 15)	3	18	16	13	11	11	10
Well controlled (1 – 6)		1	9	13	15	13	13
Itch and Hive free 0 (Zero)			4	3	3	5	5

The table illustrates the fact that during the follow-up period, a good number of people are still in mild state, indicates the drug has no sustenance.

DISCUSSION:

CSU was most common in the age group of 20-40years which is similar to the Maurer et al in which the commonest age group is 20-40 years.

The female: male ratio was 3:1 which is slightly higher than Maurer et al where the ratio was 2:1. Among females most of them were house wives.

There is no association of age or sex with angioedema, serum IgE level and Absolute eosinophil count.

The prevalence of ASST positivity in our study was 6.7% which was less when compared to the prevalence of ASST positivity in patients of chronic urticaria in various studies varing from 35 to 58%.[61-64]

There was no relationship between number of years, number of urticarial lesions and occurrence of urticaria per week.

From paired t test the following inference was made. Inj Omalizumab is effective in controlling the disease. From the pre- treatment to treatment week12 there was rapid and sustained improvement in the UAS7 score. It was foundthat during the follow up period there was a slight surge in the UAS7 score and the effectivenesss of Omalizumab was not significant. After the treatment period, there was no significant improvement in the UAS7 score. But the response varies from one another in the study population. This was similar to the study done by Maurer et al where there was a sustained improvement in the UAS7 during treatment period.[54]

The mean UAS 7 score for the entire study population drastically decreased from pre treatment period to follow up period which was similar to the ASTERIA I and ASTERIA II study.

UAS 7 has two components i.e., itch severity score and wheals score. After the administration of Inj Omalizumab it was found that there was dramatic decrease in the wheals score component of UAS7 while there was a minimal decrease in the itch severity score component. The remission period of urticaria symptoms in this study varies from 3 to 4 months in few patients when compared with ASTERIA II study where there was an average remission period of 6 to 9 months.

The adverse effect recorded in this study period was Pseudoscleroderma after the administration of omalizumab I dose. The patient was deferred Omalizumab and the patient is under investigation to find whether the adverse effect was due to omalizumab or co incidental.

CONCLUSION

Omalizumab is the third line of management in the treatment of chronic spontaneous urticaria refractory to four-fold increase in 2^{nd} generation antihistamines. In this study, a study population of 30 patients were selected by convenient sampling and after their informed consent, they were administered 3 doses of Inj Omalizumab 300mg subcutaneously once in every four weeks and the effectiveness of Omalizumab is assessed by Urticaria Activity Score 7. The patients are followed up for 3 months by the UAS7 and the data are analysed.

The conclusions of this study are

- The common age group is between 20-40 years and the female:male ratio is 3:1.
- There is no relation between angioedema, serum IgE levels and Absolute eosinophil count with either sex or age.
- The occurrence of urticaria per week, the number of years of urticaria and number of urticarial lesions per day are uncorrelated among themselves.
- There is a rapid and sustained improvement in the UAS7 during the treatment period of 12 weeks compared to the baseline UAS7. But there is no significant improvement during the follow up period.

- Most of the patients in the follow up period the patients were maintained with 2nd generation anti histamines.
- There is a dramatic fall in the wheals score of UAS7 whereas the itch severity score still persisted during the follow up period.
- One patient had pseudosclerodema following first dose of omalizumab.
- Inj Omalizumab 300mg subcutaneously can be given once in 4 weeks unless otherwise contraindicated.

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ANNEXURE - ABBREVATIONS

EAACI = European Academy of Allergy and Clinical Immunology;

GA2LEN = Global Allergy and Asthma European Network;

EDF = European Dermatology Forum;

WAO = World Allergy Organization

CSU = Chronic Spontaneous Urticaria

QOL = Quality of life

UAS7 = Urticaria Activity Score 7

ISS = Itch Severity score

SLE = systemic lupus erythematosus

EBV = Ebstein Barr Virus

NSAIDS = Non-steroidal anti-inflammatory drugs

KI = Pottasium Iodide

IgA = Immunoglobulin A

IgE = Immunoglobulin E

ELISA = Enzyme Linked Immuno Sorbent Assay

HIV = Human Immunodeficiency Virus

RPR = Rapid Plasma Reagin

ECG = Electrocardiogram

OPD = Outpatient department

Fcε R1 = Fc epsilon R1 receptor

PROFORMA

Name Age: Sex:

Occupation: Marital Status:

Address:

Phone No:

1.H/O itchy raised skin lesions:

Incidence per week:

Number of lesions:

Duration of lesions:

Resolution by:

2. itching:

3. Fever

4. Pain over lesion:

5.any contact with plants:

6. aggravation after food:

7. exacerbation after sun exposure:

8. exacerbation after cold exposure:

9. exacerbation followed by pressure:

10. exacerbation after water exposure:

11. exacerbation followed by any drugs:

12. any H/O swelling of lips

13. H/O difficulty in breathing

14. H/O swallowing of food

15. H/O any chest pain

16. H/O abdominal pain

17. H/O any infections

18. H/O loss of weight

19.H/O loss of appetite

20.H/O altered bowel and bladder habits.

21 previous treatment history

22. menstrual history

23. Personal history

24. Vitals: pulse rate: BP: RR:

25.Other system:

26. Dermatology examination

ASST:

Urticaria Severity Score 7:

Investigations:

Complete blood count:

Renal function test:

Liver function test:

Absolute eosinophil count:

Serum IgE levels:

ICTC:

HBsAg:

Anti HCV:

Chest X ray:

ECG:

Autologous serum skin test (ASST):

Thyroid profile:

தகவல் அறிக்கை

அரசு ஸ்டான்லி மருத்துவமனையில் தோல் பிரிவில் அட்ரிக்கேரியா என்ற நோய் உள்ளவர்களிடம் ஒமாலிசுமாப் என்ற மருந்தின் ஆற்றல் மற்றும் பக்க விளைவுகளை அறிதல் பற்றிய ஆய்வு நடத்தப்படுகிறது.

இந்த ஆய்வு மரு.வி.ஆனந்தன் அவர்களின் தலைமையில், மரு.சாரதா அவர்களின் உதவியோடு மரு.அனிதா கிறிஸ்டியால் நடத்தப்படுகிறது.

இந்த ஆய்வில் உங்களின் பங்கேற்பு முற்றிலும் தன்னிச்சையானது. இந்த ஆய்வில் நீங்கள் பங்கேற்பதற்கு முன்பு. இதில் உங்கள் நோய்க்கான மருந்து பற்றியும், சாத்தியமாகும் பயன்கள், பக்க விளைவுகள் பற்றியும் இந்த தகவல் படிவத்தில் உங்களுக்கு கூறப்படும்.

நாள்பட்ட நீடித்திருக்கும் அட்ரிக்கேரியா நோய்க்கு ஓமாலிசுமாய் என்ற மருந்து தோல் ஊசியாக மாதம் ஒரு முறை மூன்று மாதங்களுக்கு உங்களுக்கு அளிக்கப்படும்.

இந்த நோய் அரிப்பு, தடிப்பு ஏற்படுத்தும் IgE என்ற இம்முனோகுலோபின் என்பதற்கு எதிரதாக செயல்படுகிறது. இதனால் அரிப்பு மற்றும் தடிப்பு குறைகிறது.

உங்களின் மருத்துவ வரலாறு மற்றும் தற்போதைய ஆரோக்கிய நிலை பற்றி கேள்விகள் கேட்கப்படும். உங்களுக்கு இச்சிகிச்சை அளிக்கும் முன் சில பரிசோதனைகள் செய்யப்படும்.

மேலும் இந்த ஆய்வில் பங்கேற்பதால் கூடுதலாக எந்த பயனும், எந்த விளைவும் இல்லாமல் போகலாம். உங்களுக்கு தலைவலி, காய்ச்சல், ஊசி போடும் இடத்தில் தொந்தரவு மற்றும் அனபிலக்சிஸ் ஆகிய பக்க விளைவுகள் வர வாய்ப்பு உள்ளது. ஆனால் அந்த வாய்ப்பு மிக மிக அரிது.

அரிப்பு வரலாறு மற்றும் கடுமைத்தன்மை விவரங்கள் கையோடு மூலம் சேகரிக்கப்டும். மருத்துவரிடம் அடுத்த வருகை வரை அதை நிரப்ப உங்களிடம் எதிர்பார்க்கப்படுகிறது.

இதில் முழுமனதுடன் பங்கேற்க விரும்பினால் ஒப்புதல் படிவத்தில் கையெழுத்திடமாறு கேட்டு கொள்கிறோம்.

ASSESSMENT OF EFFECTIVENESS AND SAFETY OF OMALIZUMAB IN THE TREATMENT OF CHRONIC SPONTANEOUS URTICARIA

Investigator: **Dr. S Anitha Christy MD.D.V.L 1st yr**

Guide: **Dr.V.Anandan (Professor & H.O.D)**

Dr. Afthab Jameela Wahab (Associate Professor)

Dr K.P Saradha (Asst Professor)

Patient Information Module

You are being invited to be a subject in this study.

Before you participate in this study, I am giving the following details about this trial, which include the aims, methodology, intervention, possible side effects, if any and outcomes

All patients diagnosed with chronic urticaria will be included in this study. A detailed clinical history will be taken following a standardized proforma. A clinical examination and relevant basic investigation will be done. They will be administered omalizumab and followed up in our outpatient department for a period of 1 year at regular intervals

The result arising from this study will be analysed and used for academic purposes. You will be given clear instructions at every step and you are free to ask/clarify any doubts. Your identity remains confidential. You are free to withdraw from the trial at any point of time, without any prior notice &/or without any medical or legal implications.

I request you to volunteer for this study

Thanking You

Investigator's Sign Patient's Sign

(Dr. S Anitha Christy) Name:

URKUND

Urkund Analysis Result

Analysed Document: Assessment of effectiveness and safety of Omalizumab in the treatment of chronic spontaneous urticaria.docx (D31248421)
Submitted: 10/12/2017 12:32:00 PM
Submitted By: anitaprettyrose@gmail.com
Significance: 1 %

Sources included in the report:

10 Minu Mary Oommen.pdf (D17227386)

Instances where selected sources appear:

3

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work	:	Assessment of Effectiveness and Safety of Omalizumab in the treatment of Chronic spontaneous Urticaria.
Principal Investigator	:	Dr. S Anitha Christy
Designation	:	PG, MD DVL (Dermatology)
Department	:	Department of Dermatology Government Stanley Medical College, Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.03.2016 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

KEY TO MASTER CHART

- N.O.Y – Number of years
- UR.LE – Urticarial lesions
- D/WK – Days /week
- N.L –Number of lesions
- ANG – Angioedema
- AEC – Absolute eosinophil count
- S.I.L –Serum IgE level
- ASST –Autologous serum skin test
- LFU – Lost follow up

S.NO	AGE	SEX	OCCUPATION	N.O.Y	UR.LE		ANG	AEC	S.I.L	ASST	OMALIZUMAB												SIDE EFFECTS
					D/WK	N.L					I dose	II dose	III dose	PRE TREATMENT		TREATMENT PERIOD			FOLLOW UP PERIOD				
														wk 1	wk 2	wk 4	wk 8	wk12	wk16	wk20	wk24		
1	40	F	TEACHER	4	3	50	YES	180	298.6	+	19.1.16	20.2.16	23.3.16	33	36	13	11	9	7	10	8		NIL
2	31	m	BUSINESS	13	5	30	NO	360	405.2	-	19.1.16	20.2.16	21.3.16	40	38	20	15	14	12	12	LFU		NIL
3	41	F	HOUSE WIFE	6	7	20	NO	420	174	-	20.1.16	24.2.16	24.3.16	16	24	12	9	8	7	7	7		NIL
4	25	F	HOUSE WIFE	2	3	25	NO	722	254.5	-	27.1.16	25.2.16	29.3.16	27	31	12	11	10	8	5	5		NIL
5	38	F	HOUSE WIFE	12	4	70	NO	220	114	+	5.2.16	5.3.16	3.4.16	36	33	1	0	0	1	6	4		NIL
6	18	F	STUDENT	2	5	30	NO	443	312.6	-	7.2.16	13.3.16	17.4.16	16	21	8	6	6	3	LFU	LFU		NIL
7	35	F	COOLIE	4	6	35	NO	194	537	-	8.2.16	8.3.16	7.4.16	31	31	11	7	7	8	8	7		NIL
8	45	F	HOUSE WIFE	3	5	40	YES	296	766.3	-	24.2.16	26.3.16	24.4.16	27	28	13	9	4	3	3	3		NIL
9	30	M	COOLIE	5	6	50	YES	240	253.8	-	26.2.16	1.4.16	30.4.16	35	33	9	9	8	6	LFU	LFU		NIL
10	21	F	STUDENT	1	5	40	NO	304	715.3	-	18.7.16	18.8.16	18.9.16	26	26	4	4	3	3	2	1		NIL
11	41	F	HOUSE WIFE	8	4	20	NO	400	119.8	-	28.7.16	29.8.16	29.9.16	28	34	3	1	2	6	9	12		NIL
12	32	F	HOUSE WIFE	3	2.3	60	NO	230	321.4	-	29.7.16	29.8.16	29.9.16	14	16	9	7	5	4	4	4		NIL
13	29	F	TEACHER	2	7	25	NO	228	112.3	-	2.8.16	1.9.16	30.9.16	15	14	3	0	1	1	0	0		NIL
14	47	f	HOUSE WIFE	7	7	35	NO	40	124.2	-	19.8.16	19.9.16	19.10.16	38	34	12	6	9	9	14	14		NIL
15	45	F	COOLIE	20	7	70	NO	146	239	-	17.8.16	19.9.16	19.10.16	27	32	11	10	9	8	14	15		NIL
16	58	F	HOUSE WIFE	2	6	50	NO	88	25.8	-	19.8.16	19.9.16	17.10.16	14	16	1	0	0	0	1	1		NIL
17	32	M	PLUMBER	6	4	30	NO	189	814.3	-	31.8.16	3.10.16	4.11.16	38	40	10	7	7	7	7	7		NIL
18	38	F	HOUSE KEEPE	3.5	7	60	NO	445	692	-	19.9.16	1.11.16	3.12.16	35	32	14	11	9	9	9	10		NIL
19	33	M	BUSINESS	8	5	25	NO	122	156	-	17.10.16	25.11.16	29.12.16	22	26	1	1	1	1	3	2		NIL
20	27	F	TEACHER	4	4	50	NO	118	342	-	24.10.16	23.11.16	22.12.16	27	29	9	9	7	7	7	7		NIL
21	29	M	OFFICE ASST	1	5	40	NO	400	543.3	-	28.10.16	30.11.16	30.12.16	17	14	6	3	3	2	1	1		NIL
22	18	F	STUDENT	2	6	25	NO	324	119.1	-	5.11.16	5.12.16	4.1.17	38	38	10	7	7	5	5	5		NIL
23	52	F	HOUSE WIFE	14	3	10	NO	89	231.6	-	14.11.16	13.12.16	12.1.17	18	16	7	7	5	5	4	4		NIL
24	48	F	HOUSE WIFE	7	5	50	NO	252	196.7	-	22.11.16	21.12.16	21.1.17	23	24	6	3	3	3	2	2		NIL
25	44	M	COOLIE	9	7	40	NO	218	567	-	6.12.16	5.1.17	5.2.17	27	25	10	9	6	4	4	4		NIL
26	31	F	HOUSE WIFE	3	5	20	NO	387	124	-	18.12.16	16.1.17	14.2.17	20	19	4	1	1	0	0	0		NIL
27	56	F	HOUSE WIFE	19	6	25	NO	119	328	-	4.1.17	3.2.17	4.2.17	28	26	8	6	5	3	4	4		NIL
28	23	M	STUDENT	1	4	50	NO	232	673.4	-	11.1.17	10.2.17	12.2.17	19	22	1	0	0	0	0	0		NIL
29	49	F	OFFICE ASST	6	5	80	NO	365	107.3	-	22.1.17	23.2.17	25.3.17	36	34	10	8	8	7	7	7		NIL
30	33	F	HOUSE WIFE	2	6	50	NO	443	660	-	4.2.17	DEFERRED		21	15	1	) PSEUDOSCLERODERMA						